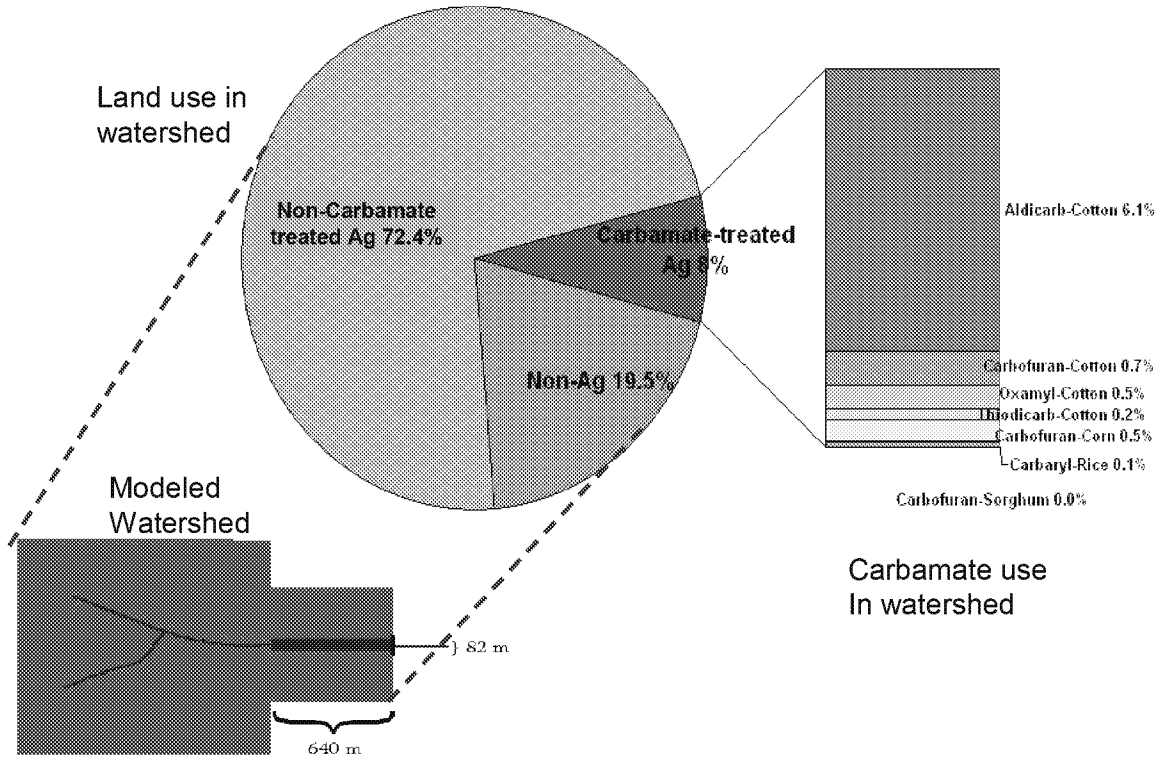
b. **Conceptual Model for Surface Water Sources of Drinking Water**

EPA identified regional surface water exposure scenarios where high NMC use areas coincided with potentially vulnerable surface water sources. The Agency bases its drinking water exposure assessment for surface-water sources on a small reservoir in an agricultural watershed. An analysis of available monitoring data indicates that such reservoirs are likely to be among the most vulnerable surface drinking water sources (FIFRA SAP, 1998; USEPA, 1999c, 2000b). The NMC CRA focused on watershed-scale impacts from multiple NMC uses occurring in multiple fields in a watershed ([REF _Ref175717475 \h * MERGEFORMAT]).

Co-occurrence of NMC pesticides in surface water sources of drinking water is based on the amount and timing of pesticide use in the watershed. EPA used county- or multi-county level pesticide use information, based on agricultural chemical use surveys (Appendix II.E.4), to identify the potential for co-occurring NMC uses in the same location. The potential for co-occurrence of NMC residues in water at the same time depends upon application timing, pesticide persistence and transport characteristics. The relative proportions of each NMC used in the watershed are based on the amount applied in a given year (a function of the rate and frequency of application, combined with the crop area treated); pesticide fate and transport properties that affect the amount of pesticide available at the surface for runoff; the runoff susceptibility of the soil; and the timing, amount, and frequency of rainfall.

Figure I.[STYLEREF 2 \s]-[SEQ Figure * ARABIC \s 2]. Conceptual model for surface water sources of drinking water illustrating how multiple NMC uses are proportioned in the watershed



For the watershed approach, OPP estimated pesticide concentrations over time (30-year simulation) for each crop-NMC combination. The temporal distributions allowed the Agency to determine the likelihood of co-occurrence of the NMCs in water over time. The Agency used regional crop areas based on USDA Ag Census data (USDA, 2002, as described in USEPA, 2000b) and acre treatments to adjust the estimated daily concentrations for each of the NMCs for the portion of the watershed that is treated by that particular NMC. These crop-adjusted concentrations are converted to a concentration equivalent for the index chemical (in this case, oxamyl) and combined into a single set of daily NMC cumulative concentrations (spanning multiple years) for each region.

For exposure from surface water sources of drinking water, the Agency used estimated concentrations derived for the source water from a reservoir, assuming no treatment effects. As noted, available studies indicate that conventional drinking water treatment processes will not fully remove NMC residues from water. At the same time, the Agency has no reason to expect that the standard drinking water treatment process will result in more toxic transformation products (see Appendix II.E.3).

c. Conceptual Model for Vulnerable Ground Water Sources of Drinking Water

The potential for pesticide movement to ground water sources of drinking water depends on such factors as hydrologic properties of the overlying soil and vadose zone that affect downward movement of water and chemicals, travel time through the unsaturated zone to ground water, aquifer properties (conductivity, porosity, depth, type, location of recharge area), the leaching potential of the pesticide (persistence and mobility), and the type of well drawing water for drinking purposes (Focazzio et al, 2002). These factors vary geographically and cause certain wells in one region to be more vulnerable than those in another region. EPA based its ground water exposure assessment on private rural wells which draw water from a shallow, unconfined aquifer (also known as a water table aquifer). In general, such drinking water sources tend to be more vulnerable than public water supply wells and provide estimates of drinking water exposure representative of people living in agricultural areas and relying on shallow wells for drinking water.

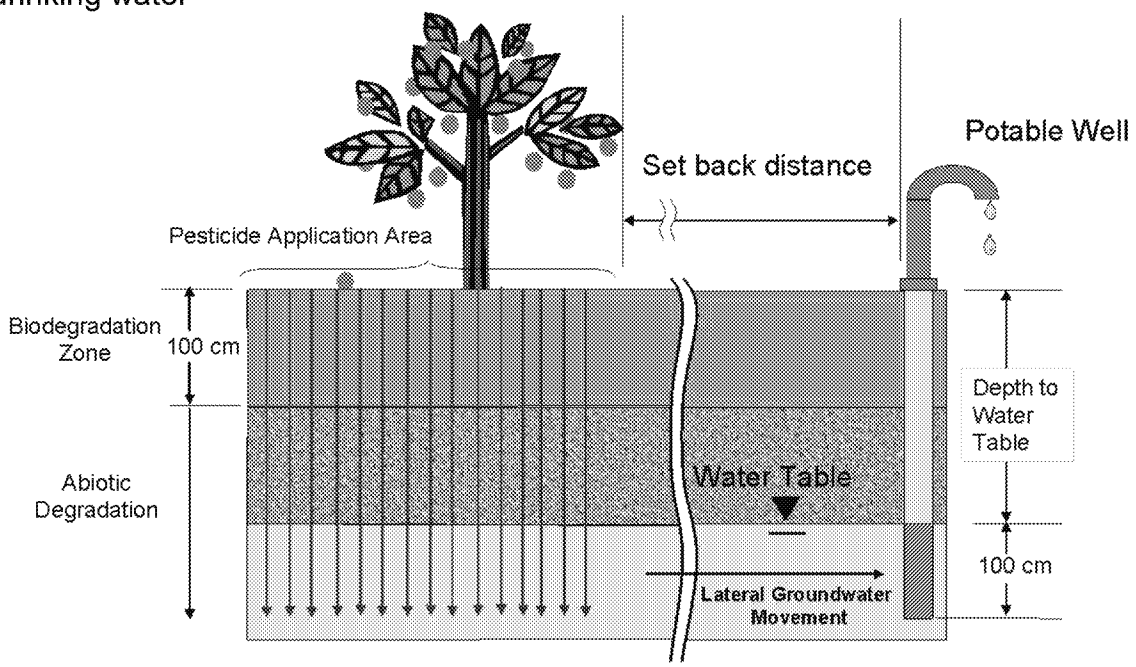
[REF _Ref175717532 \h * MERGEFORMAT] illustrates the conceptual model used to estimate pesticide transport to private wells. The pesticide is applied to the soil surface or plant canopy and precipitation or irrigation moves the pesticide through the vadose zone into a saturated zone. Simultaneously, physical and chemical properties of the individual NMCs determine the degree to which they are degraded or sorbed to soils. EPA assumed a depth to the top of a shallow, surficial aquifer of 9.1 m (30 ft) in this revised assessment. While such information is not readily available, sources ranging from USGS NAWQA (Berndt et al, 1998; McPherson et al, 2000) and ground water atlases (USGS, 1990) to FL water management districts, suggest that 30- to 50-feet is representative of the depth to shallow ground water supplying private wells. The concentration in the well is the average saturated pore water concentration across a one-meter length of the screen, extending down from the top of the water table.

Degradation occurs at different rates through the soil profile. Generally, faster degradation from microbial processes occurs in the top of the profile and decreases with depth. The model assumes that NMC degradation resulting from aerobic metabolism occurs in the top 25 cm, with rates declining linearly to 1 meter. Below a meter, only abiotic processes (in this case, hydrolysis) are simulated.

For some pesticides, well setbacks ([REF _Ref175717532 \h * MERGEFORMAT]) are specified by state or federal labels. For such cases, the additional travel time for a pesticide to reach a drinking water well and the degradation that occurs during that time is taken into

consideration by modeling lateral plug flow movement toward the well (see Appendix II.E.7 for details).

Figure I.[STYLEREF 2 \s]-[SEQ Figure * ARABIC \s 2]. Depiction of general ground water scenario concept used for estimating pesticide concentrations in drinking water



Pesticide fate properties (persistence under acid hydrolysis) and available monitoring data (Suffolk Co. Dept. of Health, 2000; USGS, 2006) indicate that several NMC residues are likely to persist in acidic ground waters. In addition, cumulative exposure in ground water is likely to reflect past as well as current uses, particularly for deep wells.

Available monitoring data, primarily from the USGS NAWQA program, confirm that more than one NMC residue may occur together in ground water (Appendix II.E.2). Co-occurrence in ground water can result when more than one NMC pesticide is used at different times on the same crop, on different crops in rotation on the same fields, or on different crops grown on adjacent fields

4. Analysis Plan

This section provides a brief description of the methods of analysis EPA used in generating the cumulative NMC concentrations in drinking water sources for use in the cumulative dietary exposure assessment. The dietary baseline analysis assumes that all carbofuran uses other than import tolerances are removed. The impacts of currently registered domestic uses of carbofuran on drinking water sources were modeled in this assessment, but results are summarized separately in a sensitivity analysis.

a. NMC Properties

The predicted persistence and movement of each NMC pesticide in the environment are based on environmental fate and transport studies submitted by the registrants as a requirement of registration and/or re-registration. Inputs for the water models are based on environmental fate data reviewed by EPA and described in the individual chemical assessments. [REF _Ref175717858 \h] summarizes the dominant persistence and mobility characteristics of the NMCs included in the drinking water exposure assessment. Appendix II.E.5 provides detailed chemical inputs used in the water exposure models. For aldicarb and its sulfoxide and sulfone degradates included in the common assessment group, the Agency used half-life values for the combined aldicarb residues (parent plus degradates) and the sorption value for the most mobile of the degradates.

Table I.[STYLEREF 2 \s]-[SEQ Table * ARABIC \s 2]. Summary of *N*-methyl carbamate fate and transport properties

Pesticide	Persistence / Degradation Pathway	Mobility / Sorption

Pesticide	Persistence / Degradation Pathway	Mobility / Sorption
Aldicarb, including sulfoxide and sulfone degradates (USEPA, 2006c, 2006d)	**Field**: Aerobic soil metabolism (55 d half-life); pH-dependent hydrolysis for degradates (2-3 d @ pH9 for sulfoxide; 60-63 d @ pH7, 6 d @pH8, 1 da @ pH9 for sulfone) **Water**: Aerobic aquatic metabolism (12 d half-life); pH-dependent hydrolysis for degradates	Kd = 0.12 mL/g (Koc = 10 mL/g)
Carbaryl (USEPA, 2003a, 2007b)	**Field**: Aerobic soil metabolism (12 d half-life); hydrolysis (12 d @ pH7, 0.1 d @ pH9) **Water**: Aerobic aquatic metabolism (30 d half-life); pH-dependent hydrolysis	Koc = 196 mL/g
Carbofuran (USEPA, 2005c, 2005d)	**Field**: Hydrolysis (28 d @ pH7, 9 d @ pH7.5, 3 d @ pH8, <1 d @ pH9); aerobic soil metabolism (321 d half-life) **Water**: pH-dependent hydrolysis	Koc = 36 mL/g
Formetanate HCl (USEPA, 2005e)	**Field**: Aerobic soil metabolism (6 d half-life); hydrolysis (24 d @ pH7,9) **Water**: Aerobic aquatic metabolism (13 d half-life); hydrolysis	Koc = 340 mL/g
Methomyl (USEPA, 1997c, 2007d)	**Field**: Aerobic soil metabolism (79 d half-life); alkaline hydrolysis (30 d @ pH9) **Water**: Aerobic aquatic metabolism (7 d half-life); hydrolysis	Koc = 24 mL/g
Oxamyl (USEPA, 1999f, 2007e)	**Field**: Hydrolysis (7 d @ pH7, 0.1 d @ pH9); aerobic soil metabolism (20 d half-life) **Water**: Hydrolysis; aerobic aquatic metabolism (40 d); anaerobic aquatic metabolism (7 d)	Koc = 6 mL/g
Thiodicarb, degrades to methomyl (USEPA, 1997d)	**Field**: Aerobic soil metabolism (2 d half-life); hydrolysis (32 d @ pH7, 0.5 d @ pH9) **Water**: Aerobic aquatic metabolism (3 d half-life); anaerobic aquatic metabolism (<1 d); pH-dependent hydrolysis	Koc = 485 mL/g

Most of the NMC pesticides exhibit pH-dependent hydrolysis (Table I.E.3). They tend to be stable or degrade slowly under acidic conditions. As the pH increases to neutral and alkaline conditions, they hydrolyze more rapidly. Unless otherwise indicated, EPA used the hydrolysis rates for acidic conditions in modeling. These rates are generally slower and would result in likely overestimates of actual exposures in neutral to alkaline conditions. Where the Agency had information that showed that the dominant pH of the soil/vadose zone/groundwater system was neutral to alkaline, hydrolysis rates (appropriate to the pH) were used.

b. Identifying Regional Exposure Scenarios

The selection of specific locations for regional drinking water assessments involves several steps. First, the Agency identified the high NMC usage areas within each region. The Agency used data collected by Thelin and Gianessi (2000) for county-level estimates of NMC usage. EPA evaluated the relative high NMC use areas several different ways:

- Summing total pounds of each NMC by county to calculate both total pounds of NMC pesticide per county and total pounds per acre;

- Adjusting the county-level estimates of pounds of each NMC by their respective relative potency factors to identify areas of greatest use of the most potent of the NMCs;

- In addition, for ground water exposure, identifying the aldicarb and carbofuran use areas, which were driving NMC exposure, to determine if additional scenarios were needed and for sensitivity analysis.

Next, EPA identified the types of drinking water sources in each high usage area. The Agency used a spatial dataset that describes water use for all the counties in the continental US (USGS, 1999) to determine the dominant source of drinking water – (1) public supply served by surface water, (2) public supply served by ground water, or (3) domestic self-supplied drinking water (primarily private wells). For surface water exposures, the Agency overlaid the public surface water supply data, along with locations of drinking water intakes (based on SDWIS data), with the NMC use maps to identify counties in which high NMC use coincided with surface water sources of drinking water. For ground water exposures, the Agency focused on private wells, which are generally shallower than public supply wells and typically have no water treatment applied. The Agency overlaid the domestic drinking water supply data with NMC use to identify those counties where high NMC use coincided with populations drinking from private wells.

The final step in choosing regional locations for modeling was to assess the vulnerability of drinking water sources within the high NMC usage areas. For surface water sources of drinking water, OPP compared relative vulnerabilities of the areas based on average annual runoff, average 2-month runoff (beginning of the growing season), and average soil loss, as developed by the USDA Natural Resources Conservation Service (Kellogg et al, 1997). The regional drinking water scenario sites are shown in [REF _Ref175717320 \h * MERGEFORMAT] and summarized in [REF _Ref175718060 \h].

Table I.[STYLEREF 2 \s]-[SEQ Table * ARABIC \s 2]. Regional drinking water exposure sites and dominant NMC pesticide uses

Region	Exposure scenario sites (1)	Dominant use crops	NMC pesticides used (2)
Southeast	NC coastal plain (SW, GW), eastern GA (SW), southern GA (GW)	Cotton, peanuts, tobacco, pecans	Aldicarb, carbaryl, carbofuran, methomyl, oxamyl

Region	Exposure scenario sites (1)	Dominant use crops	NMC pesticides used (2)
Florida	South FL (SW), Central FL (GW, SW), Northeastern FL (GW)	Citrus, sweet corn, sugarcane, cucumber, pepper, potato	Aldicarb, carbaryl, carbofuran, methomyl, oxamyl, thiodicarb
Mid-south	Northeast LA (SW)	Cotton, corn, sorghum	Aldicarb, carbofuran, oxamyl, thiodicarb
North / north central	South central PA (SW), Central IL (SW), Delmarva (GW) (3)	Apples, corn, peaches, sweet corn, alfalfa, pumpkin, potato, beans, cucurbits	Carbaryl, carbofuran, formetanate HCl, methomyl, oxamyl, thiodicarb
Lower Midwest	Southern tip of TX (SW)	Grapefruit, cotton, vegetables	Aldicarb, carbofuran, formetanate HCl, methomyl, oxamyl
Northern Great Plains	Red River Valley (SW)	Potatoes, sugar beets, wheat	Aldicarb, carbaryl, carbofuran, oxamyl
Northwest	Central WA (SW, GW)	Potatoes, apples, cherries, beans, carrots, onions	Aldicarb, carbaryl, carbofuran, formetanate HCL, methomyl, oxamyl
Southwest	CA Central Valley (SW)	Citrus, stone fruit trees, cotton, melons, grapes, tomatoes, various cole, root, tuber vegetables	Aldicarb, carbaryl, carbofuran, formetanate HCl, methomyl, oxamyl

(1) SW = surface water scenario site; GW = ground water scenario site
(2) EPA proposed canceling all domestic uses of carbofuran; carbofuran model results are presented as separate sensitivity analysis.
(3) The Delmarva scenario was used for the carbofuran sensitivity analysis only.

For potentially vulnerable ground water sources of drinking water, EPA relied on a variety of sources, including Nolan et al (2002), USGS NAWQA reports and Ground Water Atlases, USDA/NRCS county soil datasets (SSURGO), and other state/local information. EPA also used monitoring data from Florida (FL DEP, 2005; USGS, 2006) to identify specific site, soil, and hydrologic properties that might serve as indicators of potential high NMC exposure conditions. Regional ground water exposure scenario sites are listed in.

c. **Regional Usage**

The regional exposure areas of interest consist of multi-county areas that encompass the vulnerable drinking water source in high NMC use areas. EPA collected information on the target crops, estimated NMC usage, and timing of application for these multi-county areas.

The drinking water exposure assessments require information on crop use, pounds applied, application rate, number of applications, percent of crop treated, and application timing. Much of this information is not easily available or does not exist at the geographic scale needed

for the exposure assessment. As a result, EPA used the best available information to provide the regional estimates for the NMC pesticide-crop combinations that actually occur in scenario areas. Because county-level pesticide usage data is based on surveys and is uneven in quality, EPA created county clusters that surrounded the initial scenario areas shown in Figure I.E-1. EPA also used multiple data sources and multiple years of data to improve the robustness of the use data.

For each regional scenario site, EPA used USDA National Agricultural Statistics Service (USDA NASS) and Doane's databases to estimate usage (acres planted, total pounds used, percent of crop treated, application rate, and number of applications) for each NMC and crop reported in the use cluster. Usage was averaged for the years 1998 through 2002. The Agency identified those NMC-crop uses that accounted for at least 95% of the total NMC usage in the scenario area.

For the crop/chemical combinations identified in a given area, USDA crop profiles, typical planting/harvesting dates and various other sources were used to identify most likely windows of application for each use. Typically, all the NMC pesticides discussed here target multiple pests or pests that can occur multiple times during a given crop's growing season, so applications often occur over a broad time period. EPA systematically selected the beginning of the most active window for the initial application date of each NMC. Where multiple applications were identified, the Agency spread those evenly over the most active window. Details of the methods and resulting regional usage information can be found in Appendix II.E.4.

d. **Surface Water Exposure Assessment**

The Agency estimated the daily drinking water exposure from surface water sources using the simulation models PRZM (Pesticide Root Zone Model) and EXAMS (EXposure Analysis Modeling System). With PRZM/EXAMS modeling for a drinking water reservoir, the Agency can:

- Account for potential co-occurrence of NMC residues by modeling all uses in a region/area, as described in the conceptual model
- Combine daily time series over multiple years (using 30 years of recorded weather data) to account for year-to-year variations in weather and to separate peak concentrations that are not likely to occur together in time

- Estimate peak concentrations (on a daily time step); adjustments to pesticide use inputs ("typical" rates, frequencies) reflect estimated concentrations in a "typical" year

- Model vulnerable surface water sources in regions to reflect spatial variations in crops, use, weather, soils, and hydrology

- Adjust for crop area, acres treated in order to prevent double-counting overlapping uses

A detailed description of the models is available from the EPA OPP Water Models web site (USEPA, 2007f).

The model estimates daily pesticide concentrations in surface water sources of drinking water (a reservoir) using local soil, site, hydrology, and weather characteristics along with pesticide application and agricultural management practices, and pesticide environmental fate and transport properties. The input parameters are specific for each NMC-crop scenario in each region. For example, in the eastern North Carolina exposure site representing the Southeast region of the US, the cotton, peanut, and tobacco scenarios consist of properties for soils on which the crops are grown in the coastal plain of North Carolina. The weather data used in the simulations come from 30 years of weather collected at a NOAA weather station in Raleigh/ Durham, just west of the scenario area. Appendix II.E.6 provides details on the site-specific inputs for the surface water exposure.

The cumulative assessment focuses on the likelihood of concurrent exposure to multiple pesticides from food, water, and residential use. This involves using average application rates, average numbers of applications, and estimates of acres treated to adjust concentrations, and specific application windows so that only those NMC pesticides that have overlapping use periods may potentially occur together in water. The implications of these assumptions are discussed in the risk characterization chapter.

PRZM is a field-scale model, while the cumulative water assessment focuses on watershed-scale impacts (i.e., the contributions of multiple NMC uses on multiple crops occurring in multiple fields in a watershed). The Agency used PRZM to model multiple fields in a watershed. While this approach provides a more realistic depiction of multiple chemical usage in a watershed, it provides no spatial context for those fields. It also assumes that the runoff from each of those fields goes into the reservoir.

To adapt PRZM for this watershed approach, EPA adjusted the estimated pesticide concentrations generated for each crop-NMC combination to account for the portion of the watershed treated by a particular NMC pesticide:

- The NMC-crop combination was modeled with PRZM/EXAMS, using the region-specific usage, application timing, soil, site, and weather data. The result is a time-series of daily pesticide concentrations in a reservoir spanning a 30-year period.

- Each daily concentration is adjusted by the fraction of the watershed occupied by the crop being modeled. The fraction is calculated by dividing the acres of crop grown in the multi-county region by the total acres in that region (percent crop area).

- The daily concentrations are then adjusted by the fraction of acres of the crop treated by the particular pesticide. The fraction is calculated by dividing the acres of crop treated by the total crop acres in the multi-county region (percent crop treated).

The resulting concentrations for each crop-NMC combination must be converted to a concentration equivalent for an index chemical. The concentrations were normalized to an index equivalent by multiplying each of the daily concentrations by the relative potency and FQPA safety and inter-species factors for the respective NMC pesticide. The normalized outputs for each crop-NMC combination were summed day-by-day to give a daily time series of total NMC residues in water over 30 years.

e. **Ground Water Exposure Assessment**

EPA used the Pesticide Root Zone Model (PRZM) to estimate NMC concentrations in ground water sources of drinking water. Specifically, the ground water exposure assessment must account for:

- **Variations in Residues Over Time**: Pesticide residues in ground water are likely to fluctuate less drastically than residues in surface water; however, the dietary exposure estimates require a concentration time series for co-occurrence in time.

- **Variations in Residues Over Location**: As with the surface water assessment, EPA focused on regional ground water sources of drinking water that are expected to be among the most vulnerable to NMC contamination based on soil, geology, hydrology, climate, crops, and usage.

- **Co-occurrence**: USGS NAWQA monitoring shows that co-occurrence of NMC residues, though infrequent, does occur in ground water. Therefore, EPA estimated ground water concentrations for multiple NMC pesticides in ground water, based on regional usage data.

The model simulates pesticide movement through the soil and underlying vadose zone to a saturated zone, representing the surficial aquifer, at a depth of 30 feet (see [REF _Ref175717532 \h * MERGEFORMAT]). The saturated zone can be created in PRZM by setting the field capacity input parameter equal to the porosity. Output concentrations are the average from the top of the saturated zone to a depth 1 meter below the water table.

Because co-occurrence of NMC residues in ground water is likely to be more localized than for surface water, EPA considered co-occurrence based on the potential for more than one NMC to be used at different times on the same crop or on different crops in rotation on the same fields. This resulted in less crop-chemical combinations than for the surface water scenarios, which encompassed a larger area of contribution (watershed rather than fields). The Agency modeled multiple NMC uses on a crop at the same ratio of pounds used as that reported in the usage summary for the region.

As with surface water, the concentrations for each crop-NMC combination was converted to a concentration equivalent for an index chemical based on the relative potency and FQPA safety and inter-species factors. The adjusted concentrations were summed day-by-day for a cumulative time series of NMC residues in ground water distribution.

Appendix II.E.7 provides details on groundwater scenario development, model inputs, and comparisons with monitoring. It also provides site-specific inputs for the ground water model scenarios.

5. NMC Concentrations in Surface Water Sources of Drinking Water

The Agency estimated drinking water concentrations for individual and cumulative NMC load for each of the regional surface water scenario sites listed in[REF _Ref175718060 \h]. Details and results of these exposure estimates can be found in Appendix II.E.6.

a. Individual NMC Levels in Surface Water

Estimated peak concentrations of the individual NMC pesticides in each of the regional surface water scenario sites were in the sub-parts

per billion range ([REF _Ref175718314 \h]), except for aldicarb, which had estimated peaks as high as a single part per billion in the NC coastal plain scenario. Aldicarb had the highest estimated peak concentrations in 4 scenarios (NC coastal plain, GA coastal plain, central FL, northeast LA), methomyl in 5 scenarios (south FL, south-central PA, central WA, CA Central Valley, south TX tip), and carbaryl in 2 scenarios (central IL, Red River Valley, MN/ND).

Table I.[STYLEREF 2 \s]-[SEQ Table * ARABIC \s 2]. Estimated peak concentrations for NMC residues for the regional surface water drinking water scenarios (30-year period)

Region / Scenario	Pesticide	Crops	Concentration, ug/l (ppb)		
			Max.	99th %ile	95th %ile
SE: NC coastal plain	Aldicarb	cotton, peanut, tobacco	1.26	0.28	0.06
	Carbaryl	cotton, peanut, cucumber, tobacco	0.04	0.02	0.007
	Methomyl	peanut, tobacco	0.03	0.004	0.001
	Oxamyl	peanut	0.23	0.008	0.002
SE: GA coastal plain	Aldicarb	cotton, peanut, pecan	0.37	0.09	0.02
	Carbaryl	pecan	0.05	0.01	0.004
Florida (South)	Aldicarb	oranges, grapefruit	0.02	0.004	0.001
	Carbaryl	oranges, grapefruit	0.01	0.002	0.001
	Methomyl	sweet corn, pepper, cucumber	0.63	0.18	0.08
	Oxamyl	pepper, oranges, cucumber	0.14	0.02	0.006
	Thiodicarb	sweet corn	0.06	0.007	0.003
Florida (Central)	Aldicarb	oranges, grapefruit	0.46	0.07	0.01
	Carbaryl	oranges, grapefruit	0.11	0.03	0.009
	Oxamyl	oranges	0.05	0.008	0.002
Midsouth (northeast LA)	Aldicarb	Cotton	0.70	0.14	0.02
	Methomyl	thiodicarb degradate (cotton)	0.34	0.05	0.009
	Oxamyl	cotton	0.19	0.01	0.001
	Thiodicarb	cotton	0.08	0.003	0.001
Northeast/ Central (south central PA)	Carbaryl	apple, peach, sweet corn	0.02	0.003	0.001
	Formetanate	apple	0.001	<0.001	<0.001
	Methomyl	apple, peach, potato, sweet corn	0.07	0.02	0.006
	Oxamyl	apple	0.003	<0.001	<0.001
	Thiodicarb	sweet corn	<0.001	<0.001	<0.001
Northeast/ Central (IL)	Carbaryl	corn, sweet corn	0.04	0.01	0.003
	Methomyl	lima beans	0.02	0.002	0.001
Lower Midwest (South TX tip)	Aldicarb	Grapefruit, cotton	0.07	0.02	0.005
	Formetanate	Grapefruit	0.04	0.008	0.001
	Methomyl	Onions, cucumber, spinach	0.21	0.03	0.01
	Oxamyl	Cotton, carrots, onions, cucumber, cantaloupe, watermelon, peppers	0.19	0.07	0.02
Northern Great Plains	Aldicarb	Potatoes, sugar beets	0.004	0.001	<0.001
	Carbaryl	Spring wheat	0.10	0.02	0.007

Region / Scenario	Pesticide	Crops	Concentration, ug/l (ppb)		
			Max.	99th %ile	95th %ile
(Red River Valley)	Oxamyl	Potatoes	0.003	0.001	<0.001
Northwest (Central WA)	Aldicarb	Beans, potatoes	0.03	0.01	0.002
	Carbaryl	Apples, Cherries	0.04	0.004	0.003
	Formetanate	Apples	<0.001	<0.001	<0.001
	Methomyl	Beans, sweet corn	0.09	0.01	0.006
	Oxamyl	Carrots, onions, potatoes	0.02	0.005	0.003
Southwest (CA Central Valley)	Aldicarb	Cotton, beans/peas, potatoes	0.08	0.02	0.001
	Carbaryl	Apples, cantaloupe, cotton, nectarine, oranges, peaches, pistachios, plums	0.02	0.005	0.002
	Formetanate	Grapefruit, lemons, nectarine, oranges, plums, tangerines	0.03	0.004	0.001
	Methomyl	Alfalfa, asparagus, broccoli, cantaloupe, carrots, garlic, lettuce, nectarine, onions, oranges, peaches, potatoes, sugar beets, tomatoes, watermelon	0.40	0.08	0.03
	Oxamyl	Cantaloupe, cotton, garlic, oranges, peaches, tomatoes	0.02	0.01	0.005

A comparison with available surface water monitoring data (Appendix II.E.I) indicates that the estimated peak NMC residues are similar to or less than the maximum reported detections from NAWQA, with a couple of exceptions where reported NAWQA detections were greater.

- Estimated maximum aldicarb residues (parent, sulfone, sulfoxide) are similar to maximum reported detections in the southeast (NC, GA, FL). Maximum and upper percentile estimates for total aldicarb residues for the Mid-South were less than the maximum detection reported in the region (Mississippi Embayment study unit) for aldicarb sulfoxide, but greater than the 99th percentile of detections. However, even if if the modeled peak was adjusted by the difference (2.5X), the resulting cumulative NMC exposures would still be below drinking water levels of concern.

- Estimated carbaryl concentrations were less than reported detections in NAWQA, primarily because the NMC cumulative scenarios were not focused on the highest carbaryl use areas. However, the impact of this on overall NMC cumulative exposures is not expected to be significant because carbaryl has a lower adjusted RPF than do the other NMC pesticides estimated to dominate exposure in source drinking water.

- Estimated methomyl and oxamyl concentrations were similar to maximum reported detections in NAWQA.

Overall, the estimated NMC concentrations in surface water are similar to or less than reported peak concentrations from monitoring data in the same or similar regions.

b. **Cumulative NMC Levels in Surface Water**

The highest estimated cumulative NMC concentrations in surface water sources of drinking water occurred in the southern United States ([REF _Ref175718420 \h]), with the highest estimated peak following the trend: Eastern NC > northeastern LA > south FL > central FL = central IL > southeast GA. The concentrations in [REF _Ref175718420 \h] reflect adjustments for individual chemical FQPA safety and inter-species factors in addition to relative potencies. Thus, the concentrations cannot be directly compared to measured values in the environment.

Table I.[STYLEREF 2 \s]-[SEQ Table * ARABIC \s 2]. Percentile concentrations for estimated NMC cumulative distributions in the surface water scenario sites (30-year period), adjusted for relative potency, inter-species and FQPA safety factors for children

Region/Site	Percentile concentration in ug/L (oxamyl equivalents, adjusted for uncertainty factors)						Major contributors[1]
	Max	99th	95th	90th	75th	50th	
Florida / South	8.5	2.5	1.0	1.0	0.2	0.03	Methomyl, thiodicarb, oxamyl
Lower Midwest / TX	2.8	1.0	0.4	0.3	0.1	0.03	Aldicarb, formetanate, methomyl, oxamyl
Midsouth / LA	12.6	2.9	0.5	0.2	0.03	0.002	Aldicarb
Southeast / NC	20.2	4.4	1.0	0.4	0.02	<0.001	Aldicarb
Southwest / CA	4.3	1.0	0.4	0.2	0.1	0.03	Aldicarb, formetanate, methomyl
Florida / Central	7.3	1.2	0.2	0.09	0.02	0.004	Aldicarb
Northeast-central / IL	0.2	0.04	0.01	0.007	0.002	<0.001	Carbaryl, methomyl
Southeast / GA	5.9	1.5	0.3	0.09	0.02	<0.001	Aldicarb
Northeast-central / PA	0.7	0.2	0.06	0.04	0.02	0.006	Methomyl
Northwest / WA	1.3	0.3	0.1	0.07	0.03	0.007	Aldicarb, methomyl, oxamyl
N. Great Plains/ MN-ND	0.3	0.06	0.02	0.01	0.001	<0.001	Carbaryl

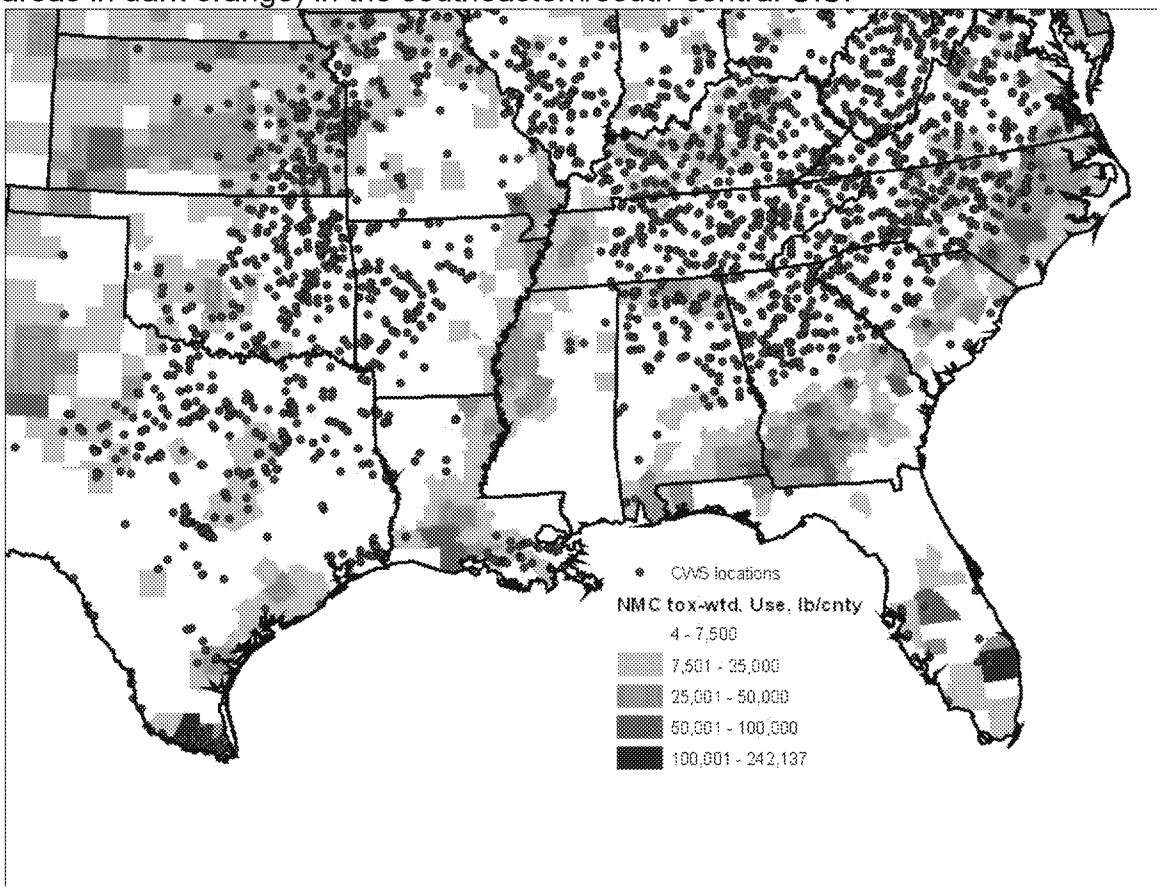
[1]Major contributors, after adjusting concentrations for relative potency and FQPA safety and inter-species factors.

c. **Spatial Extent of NMC Exposures in Surface Water**

Many surface water sources of drinking water in the southern portions of the US occur where total NMC pesticide use is relatively low ([REF _Ref175718500 \h * MERGEFORMAT]). The watersheds that are most vulnerable to runoff in the high NMC use areas tend to occur in

areas where ground water is the dominant source of drinking water. For these southern regional scenarios (Southeast, Florida, Mid-south, Lower Midwest), the estimated exposures represent a few drinking water intakes located in relatively high NMC use watersheds.

Figure I.[STYLEREF 2 \s]-[SEQ Figure * ARABIC \s 2]. Location of surface water intakes (blue dots) in relation to relative NMC pesticide usage (high use areas in dark orange) in the southeastern/south-central U.S.



The south Florida scenario represents a handful of community water systems (CWS) around the Everglades Agricultural Area (EAA). Dominant uses are sugarcane, vegetables (sweet corn, pepper, cucumber), and citrus. Drainage canals from sugarcane fields and other agricultural areas in and around the EAA are not used directly for drinking water, but eventually feed water bodies used in southern Florida for drinking water supply. Three community water systems (CWS) draw from the southern end of Lake Okeechobee. The city of West Palm Beach draws water from Clear Lake, which is fed in part by drainage water from the EAA.

The North Carolina and Georgia surface water sites represent high NMC use areas within the coastal plain from southeastern Virginia to southeastern Alabama. The dominant NMC uses in the region are on

cotton, peanuts, and tobacco. A few CWS occur in this area; many are located to the west, with watersheds draining relatively low NMC use areas.

The high-use region around northeastern Louisiana and west central Mississippi has few surface water intakes, but represents the most vulnerable area in the Mid-south region in terms of NMC usage and runoff vulnerability. Transport of pesticides in surface water is complicated by levees on the Mississippi River and a system of drainage canals. Consequently, the surface water assessment scenario is likely to be health-protective for other CWS in lower NMC-use areas in the region.

The scenario for the southern Texas tip represents a number of small CWS intakes that draw from channels in a highly-irrigated agricultural area.

d. **Sensitivity Analysis: Carbofuran in Surface Water**

Including carbofuran in regional surface water modeling would impact modeled surface water exposures, as carbofuran was a major contributor to cumulative NMC concentrations in a number of regions. The estimated peak concentrations of the carbofuran were in the same range as other individual NMC pesticides (the sub-parts per billion range). Table I.E-7 summarizes the estimated carbofuran concentrations in the regional scenarios. In comparison to the NMC concentrations in [REF _Ref177529304 \h], carbofuran had the highest estimated peak concentrations in 4 scenarios (south FL, south-central PA, central IL, south TX tip); when carbofuran was removed the NMC that replaced it was methomyl (3 scenarios) or carbaryl (1 scenario), with the maximum estimated concentration differing by less than 0.2 ppb.

Table I.[STYLEREF 2 \s]-[SEQ Table * ARABIC \s 2]. Estimated peak concentrations for carbofuran residues for the regional surface water drinking water scenarios (30-year period)

Region / Scenario	Crops[1]	Concentration, ug/l (ppb)		
		Max.	99th %ile	95th %ile
SE: NC coastal plain	Tobacco	0.002	0.001	<0.0001
Florida (South)	sugarcane, sweet corn, cucumber	0.82	0.18	0.08
Midsouth (northeast LA)	cotton, corn, sorghum	0.33	0.15	0.07
Northeast/ Central (south central PA)	alfalfa, corn, pumpkin, sweet corn	0.09	0.02	0.008
Northeast/ Central (IL)	alfalfa, corn, sweet corn	0.11	0.04	0.01
Lower Midwest (South TX tip)	Cotton, corn	0.35	0.17	0.07
Northern Great Plains (Red River Valley)	Potatoes, sugar beets, sunflowers	0.008	0.003	0.001
Northwest (Central WA)	Potatoes	0.04	0.02	0.005
Southwest (CA Central Valley)	Alfalfa, cotton, grapes	0.08	0.04	0.02

Region / Scenario	Crops[1]	Concentration, ug/l (ppb)		
		Max.	99th %ile	95th %ile

[1] The estimated exposures depicted here represent current uses for carbofuran. However, the Agency has proposed cancellation of all domestic carbofuran uses.

A comparison with available surface water monitoring data (Appendix II.E.I) indicates that the estimated peak NMC residues are similar to or less than the maximum reported detections from NAWQA, with a couple of exceptions where reported NAWQA detections were greater. While estimated peak carbofuran concentrations reported above were similar to or greater than reported detections in most USGS NAWQA units, they were well below the maximum reported detections (3-32 ug/l) from Zollner Creek in the Willamette Valley study unit. The maximum detections reported for Zollner Creek are of the same magnitude as the upper percentile of estimated ground water concentrations for carbofuran (see the sensitivity analysis for carbofuran in ground water below), which resulted in MOEs of less than 10. While peak concentrations of carbofuran in surface water are not expected to remain elevated for as long as those estimated in ground water, peak exposures of the same magnitude found in the monitoring might result in an MOE of less than 10. The Agency's analysis of potential carbofuran exposures in drinking water in the single chemical assessment includes scenarios with a use intensity similar to Zollner Creek but with greater rainfall.

In the remaining NMC scenarios ([REF _Ref177529341 \h]), the percentile concentrations increase, in some regions by almost an order of magnitude when currently registered carbofuran uses are incorporated. However, it did not result in NMC concentrations that resulted in MOEs of less than 10.

Table I.[STYLEREF 2 \s]-[SEQ Table * ARABIC \s 2]. Percentile concentrations for estimated NMC cumulative distributions with and without carbofuran in the surface water scenario sites (30-year period), adjusted for relative potency, inter-species and FQPA safety factors for children

Region/Site	Percentile concentration in ug/L (oxamyl equivalents, adjusted for uncertainty factors)						Major contributors[1]
	Max	99th	95th	90th	75th	50th	
Florida / South with carbofuran	54.5	12.1	5.3	2.6	0.8	0.3	Carbofuran
without carbofuran	8.5	2.5	1.0	1.0	0.2	0.03	Methomyl, thiodicarb, oxamyl
Lower Midwest / TX with carbofuran	24.5	11.7	5.0	3.0	1.1	0.2	Carbofuran
without carbofuran	2.8	1.0	0.4	0.3	0.1	0.03	Aldicarb, formetanate, methomyl, oxamyl
Midsouth / LA with carbofuran	21.9	7.5	2.4	1.1	0.3	0.03	Aldicarb, carbofuran

Region/Site	Percentile concentration in ug/L (oxamyl equivalents, adjusted for uncertainty factors)						Major contributors[1]
	Max	99th	95th	90th	75th	50th	
without carbofuran	12.6	2.9	0.5	0.2	0.03	0.002	Aldicarb
Southeast / NC	20.2	4.4	1.0	0.4	0.02	<0.001	Aldicarb
Southwest / CA with carbofuran	7.4	3.2	1.5	0.9	0.4	0.2	Aldicarb, formetanate, methomyl, carbofuran
without carbofuran	4.3	1.0	0.4	0.2	0.1	0.03	Aldicarb, formetanate, methomyl
Florida / Central	7.3	1.2	0.2	0.09	0.02	0.004	Aldicarb
Northeast-central / IL with carbofuran	7.2	2.5	0.9	0.5	0.1	0.02	Carbofuran
without carbofuran	0.2	0.04	0.01	0.007	0.002	<0.001	Carbaryl, methomyl
Southeast / GA	5.9	1.5	0.3	0.09	0.02	<0.001	Aldicarb
Northeast-central / PA with carbofuran	5.7	1.7	0.6	0.3	0.1	0.03	Carbofuran
without carbofuran	0.7	0.2	0.06	0.04	0.02	0.006	Methomyl
Northwest / WA with carbofuran	3.6	1.3	0.4	0.3	0.2	0.03	Aldicarb, carbofuran, methomyl, oxamyl
without carbofuran	1.3	0.3	0.1	0.07	0.03	0.007	Aldicarb, methomyl, oxamyl
N. Great Plains/ MN-ND with carbofuran	0.6	0.3	0.1	0.07	0.03	0.005	Carbofuran, carbaryl
without carbofuran	0.3	0.06	0.02	0.01	0.001	<0.001	Carbaryl

[1] Major contributors, after adjusting concentrations for relative potency and FQPA safety and inter-species factors.

6. NMC Concentrations in Ground Water Sources of Drinking Water

Individual NMC risk assessments and monitoring data indicate that aldicarb (primarily its sulfoxide and sulfone degradates) and carbofuran are the two NMC pesticides most likely to reach and persist in ground water sources of drinking water, especially in shallow, acidic aquifers. Three other NMC pesticides – carbaryl, methomyl, and oxamyl – may also reach ground water, but are not as likely to persist.

High NMC use areas occurred in counties where substantial portions of the population obtained their drinking water from private wells along the southeastern Coastal Plain, in Florida, and the Delmarva Peninsula. EPA also included a scenario in central Washington to represent potential exposures in the western US. Based on the conceptual model, the Agency focused on private wells drawing from the surficial aquifer in these regions. Details and results of these exposure estimates can be found in Appendix II.E.7.

a. Individual NMC Levels in Ground Water

The Agency estimated drinking water concentrations for individual NMC pesticides and for the cumulative NMC load based on high leaching potential scenarios representing specific high NMC uses in Florida, the southeastern coastal plain and the northwest (Tables I.E-4, I.E-9). Each ground water scenario reflects shallow wells in high leaching potential soils and vadose zones with ground water at a depth of 30 feet, with the exception of the northwestern scenario, which represents deeper groundwater. The estimated concentrations in [REF _Ref177529384 \h] reflect typical application rates for the NMC pesticides (Appendix II.E.4) and well setback distances specified on the existing label for aldicarb.

Table I.[STYLEREF 2 \s]-[SEQ Table * ARABIC \s 2]. Estimated concentrations for NMC residues for the regional ground water scenarios (25-year period) for ground water at 30 feet

NMC pesticide	Well setback distance	Crop(s)	Concentrations, ug/l					
			Max-imum	99th %ile	95th %ile	90th %ile	75th %ile	50th %ile
Florida Central Ridge, acidic ground water								
Aldicarb	1000 ft	Citrus	3.0	2.8	2.6	2.5	2.0	1.7
Oxamyl	0 ft	Citrus	0.7	0.7	0.5	0.4	0.3	0.2
Northeastern FL, neutral ground water								
Aldicarb	300 ft	Potatoes	1.7e-05	1.3e-05	8.0e-06	5.7e-06	2.7e-06	9.9e-07
Southern Coastal Plain - southern GA, acidic ground water								
Aldicarb	300 ft [1]	Peanuts	6.5	6.0	5.1	4.8	4.1	3.1
	500 ft [1]	Peanuts	3.7	3.4	2.9	2.7	2.4	1.8
Eastern Coastal Plain - eastern NC, acidic ground water								
Aldicarb	300 ft	Peanuts	1.3	1.2	1.1	1.0	0.8	0.6
Oxamyl	0 ft	Peanuts	0.01	0.01	0.01	0.01	<0.01	<0.01
Northwestern US - Central WA, alkaline ground water, 15-foot well depth								
Aldicarb	300 ft	Potatoes	0.001	0.001	<0.001	<0.001	<0.001	<0.001

[1] The current label for aldicarb specifies a 300-foot setback between the field of application and drinking water wells for use on peanuts. A proposed setback of 500 feet, based on the IRED (USEPA, 2006d), was modeled to determine the impact on exposure that would be expected from this modification to the label. Aldicarb use on peanuts is included in the dietary baseline assessment.

This comparison of model estimates with monitoring relies heavily on aldicarb monitoring data, as it is the most extensive. Estimated concentrations of total aldicarb residues (the parent plus its sulfoxide and sulfone transformation products) are comparable to existing monitoring data from a number of studies:

- Estimated concentrations with no setback distance between the well and field of application are similar to recent in-field monitoring concentrations from wells in and around citrus groves in the FL Central Ridge (Lake Wales Ridge) conducted by USGS and the Florida Department of Agriculture (USGS, 2006).

- Estimated aldicarb concentrations with no well setbacks were also similar to monitoring detections from the early 1990's from private wells in Florida (FL DEP, 2005). Those detections do not reflect subsequent label changes and required well setbacks. While aldicarb residues in recent years have been below the analytical limits of detection in the FL monitoring program, estimated concentrations modeled with a 1000-foot well setback are also below those limits of detection.

- A 2006 study by Bayer CropScience of private wells in selected aldicarb use areas (excluding FL) found detections of aldicarb residues in 10% of the wells, with detections as high as 2.9 ug/l (USEPA, 2007a). Because the single samples represent a snapshot of aldicarb concentrations over time, they are best compared to the median concentrations of the estimated exposures. The highest detections in the monitoring study (2.6-2.9 ug/l range) are similar to the median concentrations estimated for the southern coastal plain scenario represented by peanut use in GA.

Additional information on the monitoring studies for aldicarb is in Appendix II.E.2; more detail on monitoring-modeling comparisons can be found in Appendix II.E.7.

b. **Cumulative NMC Levels in Ground Water**

The cumulative NMC residues in the high-exposure ground water scenarios ([REF _Ref177529432 \h]) represent the combined contributions of the individual NMC residues listed in [REF _Ref177529384 \h] weighted for relative potency and uncertainty factors and converted to oxamyl equivalents. For this NMC assessment, high-exposure conditions refer to shallow wells (30 ft to ground water) extending through soils with a high leaching potential rating (according to USDA NRCS ratings) into an unconfined aquifer. Except where noted, the ground water is acidic, an environment that favors persistence of the NMC chemicals.

The greatest estimated cumulative NMC concentrations in ground water sources of drinking water occurred in the southern portions of the coastal plain (representing the coastal plain provinces of SC, GA, AL, and northern FL). Concentrations estimated in the Washington scenarios were substantially lower than those estimated in other areas. Because the concentrations in Table I.E.10 reflect adjustments for individual chemical FQPA safety and uncertainty factors in addition to relative potencies, they cannot be directly compared to measured values in the environment.

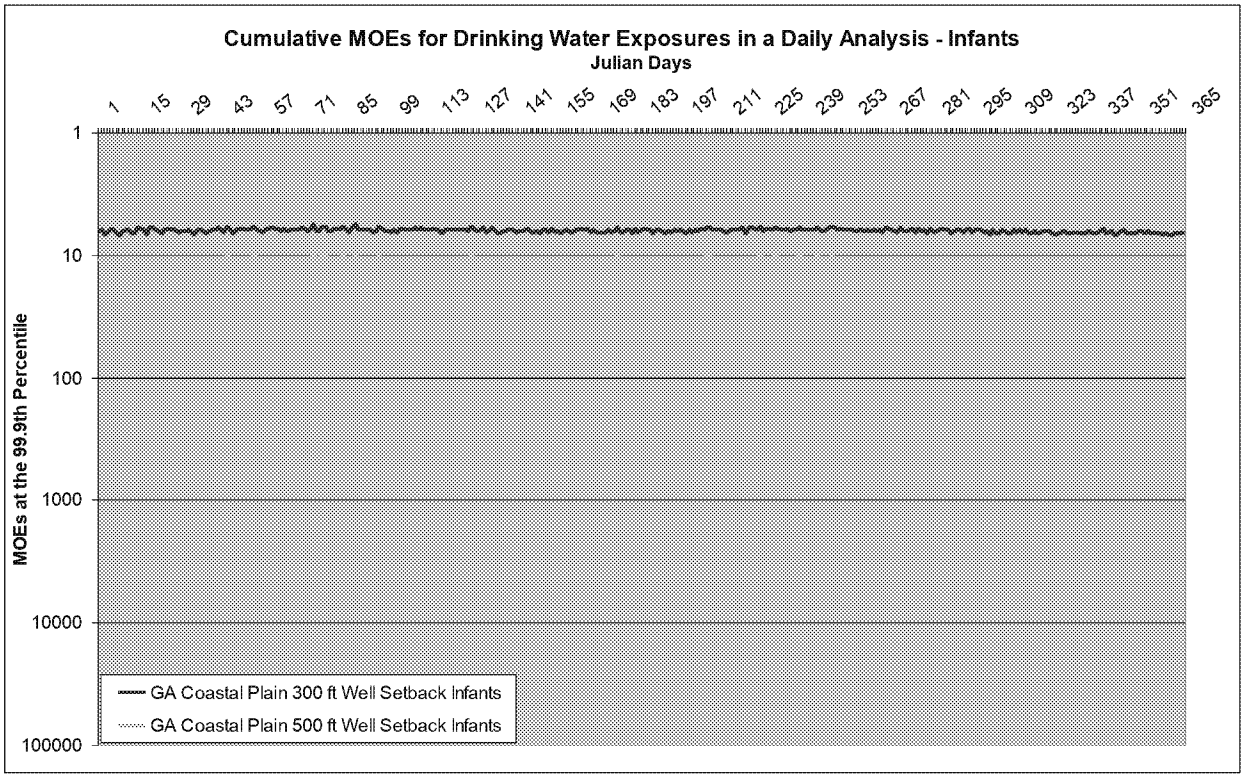
Table I.[STYLEREF 2 \s]-[SEQ Table * ARABIC \s 2]. Percentile concentrations for estimated NMC cumulative distributions in the ground water scenario sites adjusted for relative potency and using safety factors for children

Region/Site	Percentile concentration in ug/L (oxamyl equivalents, adjusted for uncertainty factors)						Major RPF/UF-adj contributor(s)
	Max	99th	95th	90th	75th	50th	
NMC Cumulative Distributions incorporating FQPA factors for children [1]							
Southern Coastal Plain / GA, 300-ft setback	104.7	96.9	82.8	76.8	66.1	49.6	Aldicarb (peanuts)
GA, 500-ft setback	59.6	55.2	47.1	43.7	37.6	28.2	Aldicarb (peanuts)
FL Central Ridge, 1000-ft setback	48.1	45.5	41.6	39.7	33.0	27.6	Aldicarb (citrus)
Eastern Coastal Plain / NC, 300-ft setback	21.6	20.0	17.5	15.7	13.5	10.3	Aldicarb (peanuts)
Northeast FL, neutral GW	2.7E-04	2.0E-04	1.3E-04	9.2E-05	4.2E-05	1.6E-05	Aldicarb, (potatoes)
NMC Cumulative Distributions incorporating FQPA factors for adults [1]							
Southern Coastal Plain / GA, 300-ft setback	52.3	48.5	41.4	38.4	33.0	24.8	Aldicarb (peanuts)
GA, 500-ft setback	29.8	27.6	23.6	21.9	18.8	14.1	Aldicarb (peanuts)
FL Central Ridge, 1000-ft setback	23.9	22.6	20.7	19.8	16.4	13.8	Aldicarb (citrus)
Eastern Coastal Plain / NC, 300-ft setback	10.8	10.0	8.8	7.8	6.8	5.2	Aldicarb (peanuts)
Northeast FL, neutral GW	1.3E-04	1.0E-04	6.4E-05	4.6E-05	2.1E-05	7.9E-06	Aldicarb, (potatoes)

[1] Concentrations have been adjusted for relative potency and inter-species factors in addition to children- or adult-specific FQPA factors.

[REF _Ref177529498 \h] illustrates the difference in exposure as a result of different well setbacks in the southern coastal plain scenario. The cumulative margin of exposure (MOE) for drinking water exposure for infants is less than 10 when the setback distance between the field and the well is 300 feet. Taking into account a larger (500-foot) well setback distance, the resulting drinking water exposure is greater than an MOE of 10. The drinking water exposure concerns are being addressed in the single chemical assessment for aldicarb. For other scenarios modeled (representing high leaching potential) the cumulative exposures for drinking water are greater than an MOE of 10 (see [REF _Ref177529655 \h * MERGEFORMAT]).

Figure I.[STYLEREF 2 \s]-[SEQ Figure * ARABIC \s 2]. Cumulative margins of exposure for drinking water from private wells in high leaching potential soils in the southern coastal plain (GA Peanuts), infants



c. Spatial Extent of High NMC Exposures in Ground Water

The ground water exposure assessment focused on areas where combined NMC exposure is likely to be among the highest within the region as a result of total NMC usage, adjusted for relative potencies, and vulnerability of the drinking water sources. Based on the fate and transport characteristics of the NMC pesticides, interpretations of existing monitoring data, and results of exposure modeling, the following conditions are likely to result in elevated concentrations of NMC residues in ground water:

- **Shallow wells**. Concentrations will vary with varying depths to ground water and well depths (the depth from which the well draws water). Higher concentrations would be expected in more shallow wells while lower concentrations would be likely in deeper wells.

- **High leaching potential soils** as classified by the USDA Natural Resources Conservation Service (USDA NRCS, 2003), with similarly permeable conditions extending through the vadose zone to ground

water. Such soils are well-drained, highly permeable, and have a low organic matter content.

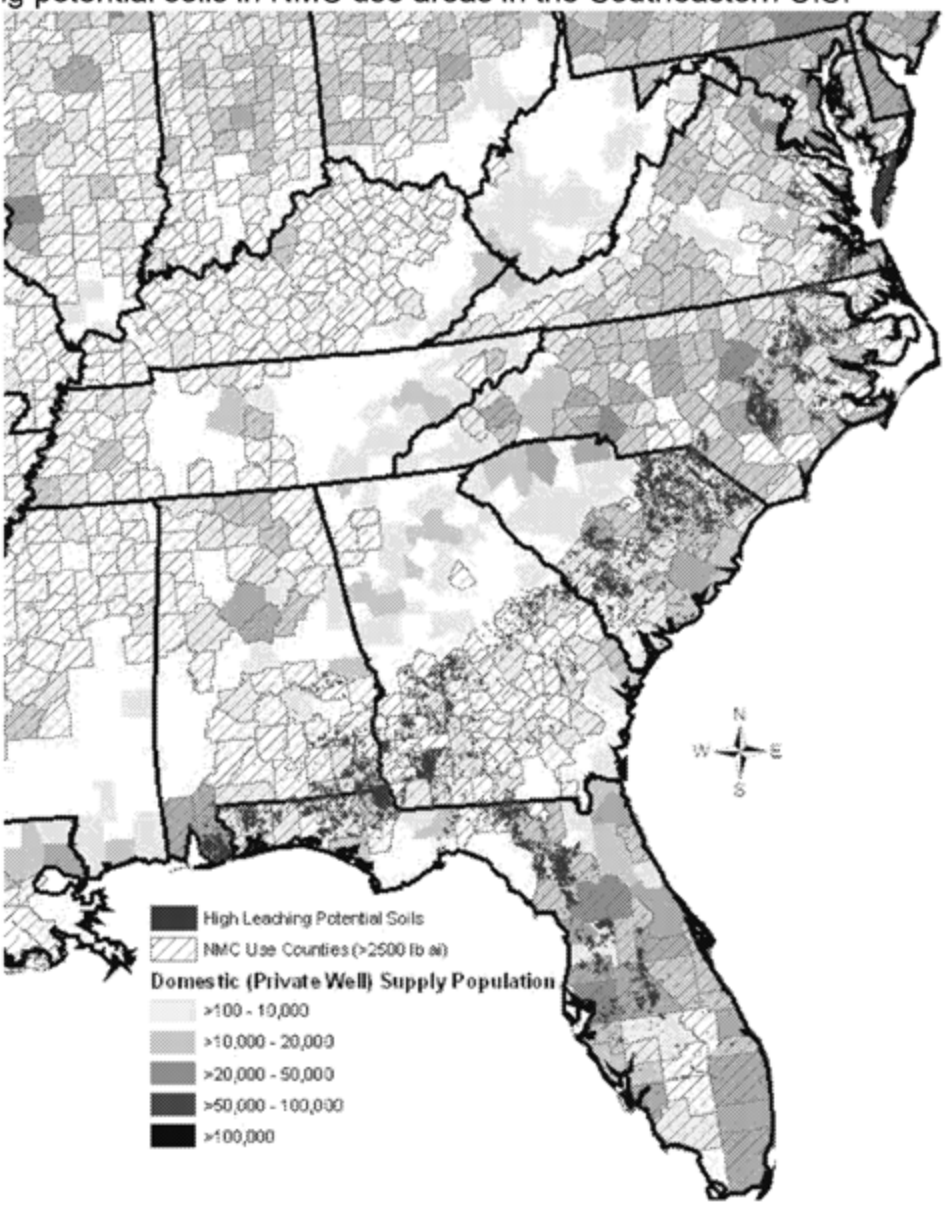
- **Acidic soil and ground water**, which favor the persistence of the NMC chemicals, particularly the sulfoxide and sulfone transformation products of aldicarb.

In most of the country, NMC residues in drinking water sources are at levels that are not likely to contribute substantially to the multi-pathway cumulative exposure. However, some areas of the Delmarva Peninsula, the southeastern coastal plain, and Florida (primarily along the central ridge) and the southeastern coastal plain have conditions that could result in elevated NMC concentrations in ground water. These areas represent what the Agency believes to be the most vulnerable private well drinking water sources for the NMCs based on available monitoring, current use patterns, and known soil and hydrologic conditions. In those vulnerable areas, which represent a relatively small area of the country, the estimated ground water residues are reasonable estimates of drinking water exposure for residents who get their drinking water from private wells that draw water from shallow depths in unconfined aquifers.

[REF _Ref175719719 \h * MERGEFORMAT] illustrates the spatial extent of high leaching potential soils (shown in red) in the NMC use areas (shown in green) in the southeastern US. Although county-level soil information was not available for the entire region at the time of the spatial assessment, such soils can be identified. While the map includes acidic, high leaching potential soils, it does not reflect depth or pH of the ground water, or the relative permeability of the underlying vadose zone and aquifer. Information on the location or depth of private drinking water wells available is also not available.

Anticipated exposures in other parts of the country are expected to be lower than surface water estimates in other regions of the country. In the north and north-central regions, total NMC use, particularly aldicarb, is relatively low. Aldicarb is no longer labeled for use in a number of northern and northeastern states because of a history of ground water contamination. In the mid-south, drinking water comes predominantly from a public ground water supply drawing from deep, protected aquifers. NMC contamination is not expected, except in an area around southeastern Missouri and northeastern Arkansas, which had several detections in the Bayer CropScience monitoring study (USEPA, 2007a). In the Great Plains and Lower Midwest, anticipated exposure is expected to be lower than surface water estimates because of low rainfall and deeper aquifers than in the southeast and Florida.

Figure I.[STYLEREF 2 \s]-[SEQ Figure * ARABIC \s 2]. Extent of high leaching potential soils in NMC use areas in the Southeastern U.S.



d. **Sensitivity Analysis: Carbofuran in Ground Water**

Carbofuran was modeled in two NMC scenarios: one representing use on potatoes in Northeastern Florida, and the other representing cucurbits in the Delmarva Penninsula in the North/North central region ([REF _Ref177529566 \h]). The Delmarva scenario was not included in the NMC assessment, but was developed specifically for the sensitivity analysis for carbofuran to represent a high-leaching potential area for cucurbit use.

Table I.[STYLEREF 2 \s]-[SEQ Table * ARABIC \s 2]. Estimated concentrations for NMC and carbofuran for regional ground water scenarios (25-year period) for ground water at 30 feet

NMC pesticide	Well setback distance	Crop(s)	Concentrations, ug/l					
			Max-imum	99th %ile	95th %ile	90th %ile	75th %ile	50th %ile
Northeastern FL, neutral ground water								
Aldicarb	300 ft	Potatoes	1.7e-05	1.3e-05	8.0e-06	5.7e-06	2.7e-06	9.9e-07
Carbofuran[1]	0 ft	Potatoes	2.7e-11	1.7e-11	9.3e-12	4.8e-12	1.5e-12	1.5e-13
Delmarva Peninsula, acidic ground water								
Carbofuran[1]	0 ft	Cucurbits, high typ. rate	38.5	36.4	28.8	25.6	20.6	15.5
	0 ft	Cucurbits, low typ. rate	10.2	9.6	7.6	6.8	5.4	4.1

[1] The Agency has proposed a cancellation of all domestic carbofuran uses. The estimated exposures depicted here represent current uses for carbofuran.

Carbofuran concentrations estimated in Northern Florida were six orders of magnitude lower than those estimated for aldicarb, and therefore would not be a significant contributor to the NMC in that region. However, carbofuran concentrations estimated on the Delmarva Peninsula are the highest estimated for any NMC. Estimated carbofuran concentrations in private wells in the Delmarva Peninsula are in line with monitoring data summarized in the 2006 Carbofuran IRED and suitable for human health exposure assessments (Appendix II.E.7).

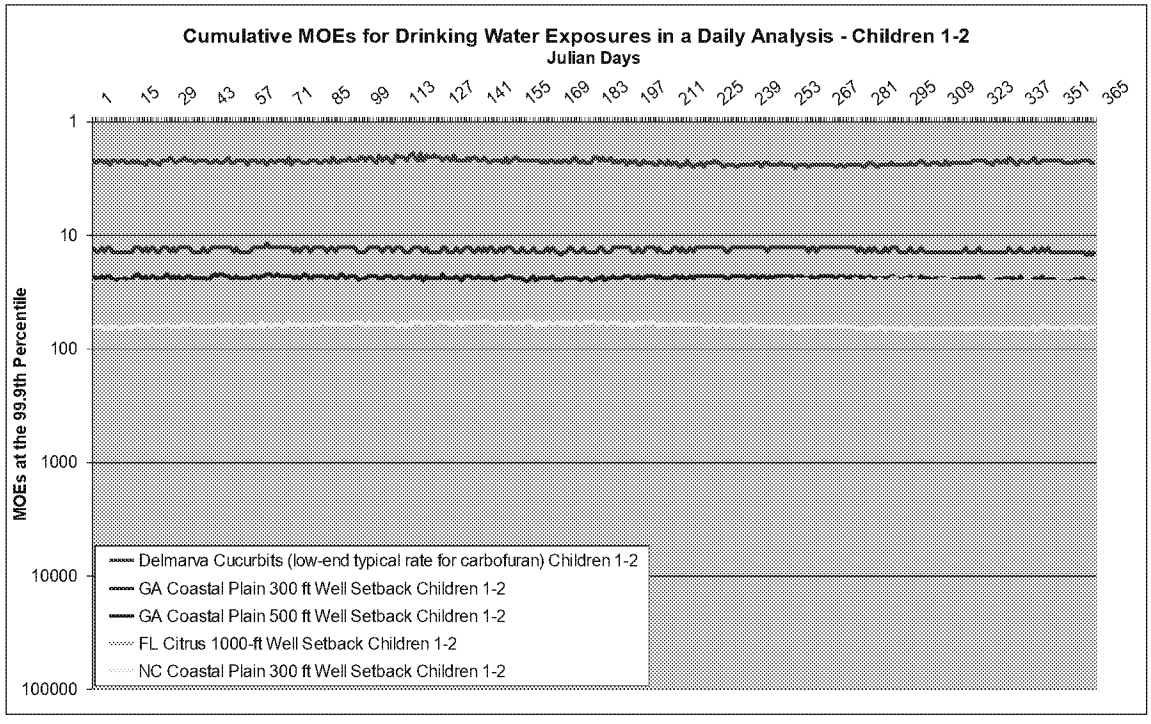
The greatest estimated cumulative NMC concentrations in ground water sources of drinking water occurred in the Delmarva Peninsula for carbofuran-driven NMC exposures ([REF _Ref177529603 \h]). The Delmarva Peninsula (carbofuran on cucurbits) would result in cumulative exposures for drinking water with a MOE of less than 10 ([REF _Ref177529655 \h * MERGEFORMAT]). These drinking water exposure concerns are being addressed through cancellation of all domestic carbofuran uses. All other estimated exposures from high leaching potential ground water sites result in MOEs greater than the target of 10.

Table I.[STYLEREF 2 \s]-[SEQ Table * ARABIC \s 2]. Percentile concentrations for estimated NMC cumulative distributions in the ground water scenario sites adjusted for relative potency and using safety factors for children

Region/Site	Percentile concentration in ug/L (oxamyl equivalents, adjusted for uncertainty factors)						Major RPF/UF-adj contributor(s)
	Max	99th	95th	90th	75th	50th	
NMC Cumulative Distributions incorporating FQPA factors for children (1)							
Delmarva / high-end typical rate	2540	2400	1898	1689	1357	1024	Carbofuran (cucurbit)
Delmarva / low-end typical rate	670.6	633.8	501.2	445.9	358.3	270.5	Carbofuran (cucurbit)
Northeast FL, neutral GW	2.7E-04	2.0E-04	1.3E-04	9.2E-05	4.2E-05	1.6E-05	Aldicarb, carbofuran (potatoes)
NMC Cumulative Distributions incorporating FQPA factors for adults (1)							
Delmarva / high-end typical rate	923.7	873.0	690.3	614.2	493.5	372.6	Carbofuran (cucurbit)
Delmarva / low-end typical rate	243.9	230.5	182.2	162.2	130.3	98.4	Carbofuran (cucurbit)
Northeast FL, neutral GW	1.3E-04	1.0E-04	6.4E-05	4.6E-05	2.1E-05	7.9E-06	Aldicarb, carbofuran (potatoes)

(1) Concentrations have been adjusted for relative potency and inter-species factors in addition to children- or adult-specific FQPA factors.

Figure I.[STYLEREF 2 \s]-[SEQ Figure * ARABIC \s 2]. Cumulative margins of exposure for drinking water from private wells in high leaching potential scenarios, children 1-2 years old



7. Summary

The drinking water assessment focuses on areas where combined NMC exposure is likely to be among the highest within each region as a result of total NMC usage and vulnerability of drinking water sources. This analysis is based on a probabilistic modeling approach that considers the full range of data and not a single high-end estimate. EPA estimated NMC exposures in drinking water to individuals in the CRA for both ground water and surface water sources of drinking water by region. The regional drinking water exposure assessments are intended to represent exposures from vulnerable drinking water sources resulting from typical NMC usage and reflect seasonal variations as well as regional variations in cropping and NMC use. Each regional assessment focuses on areas where combined NMC exposure is likely to be among the highest within the region as a result of total NMC usage, adjusted for relative potencies, and vulnerability of the drinking water sources. For ground water, private wells extending through highly permeable soil and vadose zone materials into shallow, acidic ground water are expected to be most vulnerable. For surface water, drinking water reservoirs in small, predominantly agricultural watersheds are likely to be most vulnerable. The co-occurrence of NMC residues in water is primarily estimated from modeling. Monitoring data are not available consistently enough to be the sole basis for the assessment. However, monitoring data are used to corroborate the modeling results and have helped confirm locations of potentially vulnerable drinking water sources.

In most of the country, NMC residues in drinking water sources are at levels that are not likely to contribute substantially to the multi-pathway cumulative exposure. Estimated NMC exposures from surface water sources of drinking water resulted in MOEs well in excess of 10. For most ground water sources of drinking water, NMC exposures were similarly low. Private wells in highly permeable soils that draw water at shallow depths in acidic, unconfined aquifers represent what the Agency believes to be the most vulnerable drinking water sources for the NMCs based on available monitoring, current use patterns, and known soil and hydrologic conditions. Those instances where NMC concentrations resulted in MOEs of less than 10 are being addressed with mitigation measures in the single chemical assessments – an increase in the well setback distance from 300 feet to 500 feet for aldicarb use on peanuts in the southern portion of the Coastal Plain and cancellation of all domestic carbofuran uses. With these mitigation measures, NMC exposures from drinking water result in MOEs that are greater than 10.

F. The Multi-Pathway Cumulative Assessment

The previous chapters of this document have described the development of the primary components of the risk assessment. They describe a highly complex process of combining multiple data sets to generate a description of the potential risks from NMC pesticides by each of the pathways described. OPP has had to generate new methods for each component of the assessment in order to produce an assessment, which presents as realistically as possible the potential exposure to NMC pesticides. The purpose of this chapter is to explain the concepts used to accumulate risk from each pathway into a total risk estimate, summarize some of the major revised findings, and to provide a basis for understanding the graphical temporal exposure profiles that are provided in the Appendices.

1. Basic Concepts

The definition of cumulative risk developed as a result of the passage of FQPA requires OPP to conduct a risk assessment for a group of pesticides with a common mechanism of toxicity that is multi-pathway, multi-route, and multi-chemical in scope and nature. As described in Chapter I.B of this revised cumulative assessment for the NMCs, the RPF method was used to address the issue of combining toxic responses from NMCs with varying propensities to inhibit acetyl cholinesterase. Exposure to each NMC was normalized to equivalent exposure to the index compound, oxamyl. The toxicity data currently available for conducting this analysis are estimates of response by route-specific dosing, and do not support estimating delivered dose to the target tissue. OPP decided to address this problem by comparing route-specific exposures to route-specific points of departure (PoD) to produce unitless margins of exposure for each route. Thus, each exposure route is associated with an MOE for that route. A total (or combined) MOE was calculated by taking the inverse of the MOE for each route, adding these together, and then taking the inverse of that sum. This process was used to produce a distribution of daily estimates of MOEs for the subpopulation of concern that reflects regional and seasonal variation[15] in the patterns of exposure that are likely to occur throughout the US across the year. OPP used a probabilistic assessment procedure to capture the full range of exposure possibilities from all sources analyzed. The intent was to produce an estimate of risk that is as realistic as possible. The NMC cumulative risk assessment is not a high end risk assessment for the specific situation, e.g., geographic location. OPP

[15] Note that seasonal variation was only considered for the residential and drinking water pathways. No seasonal variation was considered for the food pathway.

believes it reflects the full range of likely exposures and exposure possibilities for consideration in a regulatory context and avoids developing exposure estimates based upon combination of exposure scenarios and assumptions that are not reasonable or are unlikely to co-occur in practice. This method has been standard practice for developing total MOE estimates for aggregate and cumulative assessments and is further described in OPP's 2001 Aggregate guidance document [HYPERLINK "http://www.epa.gov/pesticides/trac/science/aggregate.pdf"]

2. Framing the Population-Based Assessment

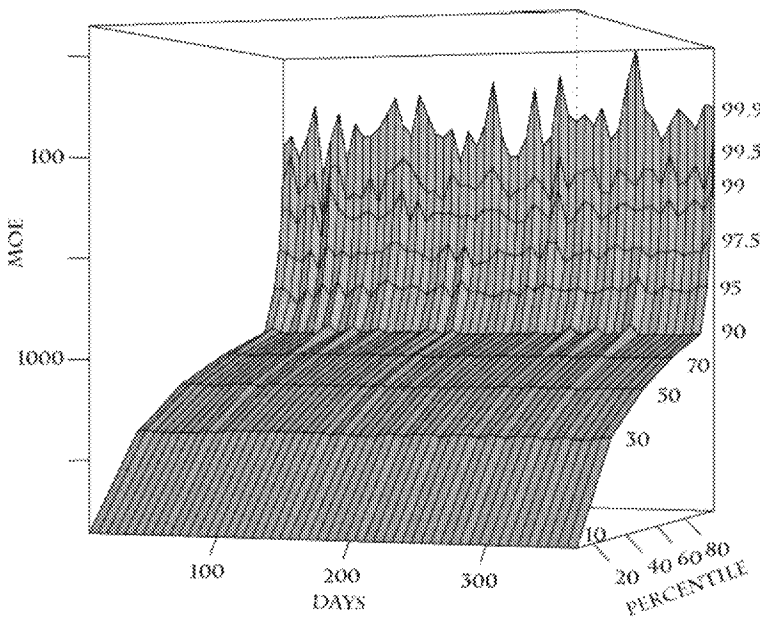
OPP used the above-described methodologies to develop a series of daily exposure distributions and array them as a distribution across time. The distribution of daily exposures and resulting MOEs are developed such that the exposures from NMCs in foods, drinking water and from residential uses are all calculated simultaneously for each hypothetical individual in the subpopulation. OPP used the Calendex software to develop the distributions and resulting MOEs. Calendex permits incorporation of time-course information with regard to residential uses of pesticides and exposures through drinking water, but does not permit specific allowance for regional variability. As described in Chapter I.E of this document, OPP addressed this issue by focusing on and developing separate assessments for regional locations that represent what is likely to be the most vulnerable drinking water sources in high NMC use areas. Based on a comparison of estimated drinking water exposures from surface- and ground-water sources in three regions as part of the preliminary NMC CRA, OPP selected drinking water exposures representing what have been determined to be the three most vulnerable areas –southern coastal plains (Georgia), Florida central ridge, and Eastern coastal plains (North Carolina) regions – for the multi-pathway assessment. NMC exposures in drinking water from the remaining parts of the country are expected to be substantially lower than from these three sites.

To generate a daily distribution of exposure for the subpopulation of interest, a consumption record is selected from the CSFII that corresponds to the age group of interest. Calendex uses this consumption record to estimate NMC exposure from food commodity by randomly assigning a residue value for each food commonly included. After multiplying each amount of food commodity consumed by its selected residue value, the total exposure for this individual from food is summed. At the same time, all appropriate residential scenarios that may be encountered for the calendar day 1 (January 1) are reviewed. A probability-based decision is made as to whether or not that scenario will be encountered (e.g., a lawn treatment; not likely in January). If the

scenario is assigned a "yes" answer, then the appropriate values defining the exposure are selected from the many distributions of input parameters for residential exposure scenarios. Dermal, oral and inhalation exposures are calculated for all selected residential scenarios. A drinking water value taken from the estimated distribution of water residues for January 1 is selected and paired with the water consumption reported in the CSFII consumption record. These values are used to calculate exposure from drinking water for that date. All of the exposures are converted to route-specific MOEs to define the total exposure to the hypothetical individual on January 1. The process is repeated for each consumption record for the age group in the CSFII one hundred times to build a distribution of exposures for January 1. This process is repeated for January 2, January 3 and so forth across the same year.

The 365 daily exposure distributions are arrayed together in order to provide a profile of possible exposures by each route and in total as MOEs. A hypothetical example of such a distribution of distributions is presented in [REF _Ref177967678 \h]. In this figure, each daily distribution is arrayed on the yz plane of the plot. Day 365 can be clearly seen on the right side of the plot. This distribution of total risk is expressed as a cumulative distribution function of MOEs versus percentile of exposure. Percentile of exposure refers to that portion of the population that has less than or equal exposure. For example, 80 % of the population has an exposure level that is equal to or less than the 80th percentile.

Figure I.[STYLEREF 2 \s]-[SEQ Figure * ARABIC \s 2]. Three-dimensional plot of the total MOE by day of the year and percentile of exposure



3. Interpreting the Outputs

The results of the final assessment are presented in graphical form in the appendices. They reflect year-long slices across the 3-dimensional plot in Figure I.F-1. In that plot, dark lines can be seen across the total MOE surface. For instance, the top line in the 3-dimensional plot represents the 99.9$_{th}$ percentile of exposure for the population. A slice through the surface parallel to the xy plane at the 99$_{th}$ percentile would look like the plot presented in Figure I.F.2. This plot presents the potential total MOE for the population exposed to NMCs by the exposure scenarios included in this assessment. In addition, the contributions from various pathways and routes of exposure are arrayed separately to assist the risk manager in identifying contributors to risk for further evaluation. Other percentiles of exposure may also be of interest.

OPP will use the changes in graphical presentations of data such as these to evaluate the significance of various sources of exposure, considering the percentile at which the exposure becomes significant and the duration over which the exposure route and source remain dominant in the risk assessment results.

4. Attributes of the Revised *N*-Methyl Carbamate Cumulative Risk Assessment

The current revised assessment focuses on estimating the potential risk from exposure to ten NMC pesticides in food and drinking water and from residential uses. The assessment is limited in geographic scope to the Southern area of the U.S. This limitation was placed on the assessment to ensure that the water and residential components of the assessment would reflect what a coherent set of pesticide uses are likely to exist. Understanding the likelihood of co-occurrence of pesticide uses is critical to developing a reasonable estimate of total cumulative risk. In the absence of direct measures of co-occurrence, overlapping exposures must be extrapolated from use data. The residential and groundwater assessments are based on the most highly exposed localized areas within the southeastern region of the United States.

As indicated previously in this report, Table I.B.7 for the food and residential components of the cumulative risk assessment, a PoD was used for the oral component of the total cumulative risk assessment. The estimated $BMDL_{10}$ (0.18 mg/kg body wt/day) for brain AChE inhibition by the index compound (oxamyl) was used. The inhalation and dermal components of the assessment were compared to $BMDL_{10}$s of 0.66 and 17.05 mg/kg body wt/day, respectively.

Integrated cumulated risk assessments were conducted for the following age groups: Children 1-2 years, Children 3-5 years, Adults 20-49 years, and Adults 50+ years of age. These four groups were chosen to emphasize the effects of differences in behavior and food consumption patterns on estimating the risk from exposure to pesticides. The assessments reflect the same assumptions about use scenarios, timing of exposures, and exposures to pesticides in food and water as used in the previous pathway specific assessments. An entire year of exposure is simulated. Three different water scenarios from the south were matched with a residential scenario that used application timing patterns that are characteristic of the South. Three water scenarios simulated ground water sources in Georgia, Florida, and North Carolina.

The food component of the cumulative risk assessment contains as many commodities as could reasonably be extrapolated from the available PDP and FDA monitoring data. This component of the assessment is regarded as highly refined and reflective of exposures likely to be encountered by the U.S. population. Because data on residential exposure are more limited, the residential component of the assessment was also designed to reflect some overestimation bias to ensure that risk from these sources of exposure were not likely to be underestimated. The water components of the assessment focused on what OPP believes are the most vulnerable drinking water sources. While the estimated drinking water concentrations are reasonable reflections of actual exposures in those particular areas, the rest of the country is expected to have substantially lower combined (or "cumulative") NMC residue levels in its drinking water.

As discussed earlier, exposure estimates are specific to the regions discussed; they take into account region-specific water and residential use practices and cannot – as a general matter – be necessarily extrapolated to different regions. The Florida central ridge groundwater scenario is specific to an area in Florida in which the use of NMC pesticides, particularly aldicarb, is high, soils are highly permeable, the depth to groundwater is shallow, and the soils and water are acidic. These conditions are favorable to potentially high levels of NMC residues in drinking water sources. The North Carolina and Georgia coastal plain groundwater scenarios represent another area where high NMC use (dominantly aldicarb), highly permeable soils, shallow ground water and acidic conditions are likely to favor potentially high combined NMC levels. Further description of these sites, conditions, and characteristics that led OPP to select these sites as high-end with respect to ground water concentrations for this cumulative assessment is in Chapter I.D of this document. OPP notes that drinking water concentrations from a combination of multiple NMCs in the much of the rest of the U.S. would be expected to be substantially lower than estimated for this

assessment. It is possible, however, that the concentration of a single NMC in drinking water could be higher than that of the concentration of that single chemical's contribution to this cumulative exposure assessment.

Estimates of cumulative risk from 10 NMCs associated with exposure through foods, drinking water, and residential uses are presented in Appendices III.F.1-24 for Children 1-2 years old, Children 3-5 years old, Adults 20-49 years old and for Adults 50+. The contributions of each of the major routes of exposure and the likely sources of those exposures are discussed in previous chapters of this revised assessment. Graphical presentations are provided for the 95th, 97.5th, 99.5th, 99th, and 99.9th percentiles but written characterizations are limited to the 95th, 99th, and the 99.9th because these percentiles capture the range of exposure which has traditionally been of most interest to the Agency. As described in the residential chapter of this document, exposures through the inhalation route were not assessed and are considered to be very small. Thus, this exposure route is not specifically discussed in each of the following descriptions.

a. **Children, 1-2 years, Georgia Coastal Plain Ground Water**

The results of the total cumulative assessment for Children 1-2 years using the $BMDL_{10}$ of the index chemical (oxamyl) for the PoD are presented in Appendix II.B.2. Temporal Exposure Profile Plots for Georgia Coastal Plain Ground Water appear in Figure III.F.2.

95th Percentile – The significant source of pesticide risk from exposure to pesticides at this percentile of exposure is through both the drinking water pathway with MOEs ranging from 117 to approximately 125 and the food component with an MOE that is generally near 142 across the year (Figure III.F.1). Dermal exposure that is associated with residential use does not occur at this percentile because typically only a small percentage of the population uses such products.

99th Percentile – The daily total MOEs ranged from 26 to 28. At this percentile, MOEs associated with food pathways were generally approximately 35 and comprise the major source for total exposure. The daily MOE values from drinking water sources ranged from 64 to 70. MOEs from oral non-dietary ingestion which are associated with residential use (i.e., hand-to-mouth) were higher than drinking water exposure and generally the MOEs for oral non-dietary exposure pathway ranged from ca. 296 to greater than 350 (Figure

III.F.1). MOEs associated with the dermal route are generally greater than 110 but as low as 99.

99.9th Percentile – At the 99.9th percentile, the total cumulative risk (all pathways) was as low as ca. 7 for this age group and nearly all of the estimated exposure came through the oral route that included significant contributions from the food pathway (Figure III.F.1). Oral non-dietary exposure (hand-to-mouth) resulted in MOEs remaining consistent through the year between ca 76 and 90. Dermal MOEs go down to 24 with an average MOE of 27.

b. **Children 3-5 years, Georgia Coastal Plain Ground Water**

The results of the total cumulative assessment for Children, 3-5 years old using the estimated $BMDL_{10}$ of the index chemical (oxamyl) for the PoD are presented in Appendix II.B.2. Temporal Exposure Profile Plots for Georgia Coastal Plain Ground Water appear in Figure III.3.

95th Percentile – Total MOEs at this percentile range from 90 to 94 throughout the year. The significant contributor to total cumulative exposure comes through the drinking water pathway (Figure III.F.3) with a range of MOEs of ca. 170 to ca. 180. The next most significant contributor to total cumulative exposure is through the food pathway; this pathway has fairly stable MOEs of slightly greater than 180.

99th Percentile – At this percentile the total (cumulative) exposure resulted in MOEs from 32 to 34 MOEs associated with food were generally near 41. MOEs from drinking water sources generally remained in the 93 to 102 range. MOEs associated with the dermal route appear for the first time here and average ca. 160. Exposures from oral non-dietary ingestion (i.e., hand-to-mouth) was less than exposure from drinking water and food and MOEs for this source generally ranged from ca. 422 to greater than 480 (Figure III.F.3). .

99.9th Percentile – At the 99.9th percentile, the total MOE (all pathways) was in the 7 to 9 range and this was nearly all contributed through food exposure (Figure III.F.3). Drinking water MOEs average 53. MOEs varied for oral non-dietary exposure around 115. MOEs from dermal exposures generally ranged between ca. 35 and 40.

c. **Adults, 20-49 years, Georgia Coastal Plain Ground Water**

The results of the total cumulative assessment for Adults, 20-49 years using the $BMDL_{10}$ for the PoD are presented in Appendix II.B.2. Temporal Exposure Profile Plots for Georgia Coastal Plain Ground Water appear in Figure III.F.6.

95th Percentile – Total MOEs at this percentile are in the 290 to 340 range with contributions from drinking water dominant and persistent throughout the year; exposures through the food pathway contribute a relatively small amount compared to total exposure, with MOEs for food above 1400 (Figure III.F.6). Dermal MOEs were all greater than 4,000.

99th Percentile – Total MOEs are generally in the 100 to 150 range at this percentile. Exposure from drinking water results in MOEs between 220 and 240 (Figure III.F.6). MOEs associated with food are generally 230. Dermal exposures are associated with MOEs of approximately 280 to greater than 2,300.

99.9th Percentile –Total MOEs at this percentile are generally in the 30-43 range, with exposure from food dominant throughout the year (Figures III.F.1-9). MOEs associated with drinking water are generally about 115. Dermal exposures are associated with MOEs of approximately 50 to greater than 500.

d. **Adults, 50+ years, Georgia Coastal Plain Ground Water**

The results of the total cumulative assessment for Adults, 50+ years using the $BMDL_{10}$ for the PoD are presented in Appendix II.B.2. Temporal Exposure Profile Plots for Georgia Coastal Plain Ground Water appear in Figure III.F.7.

95th Percentile – Total MOEs at this percentile are in the 220 to 260 range with contributions from drinking water and food contributing all year long a relatively similar exposure resulting in MOEs above 400 and dermal MOEs were all greater than 4,000 (Figure III.F.7).

99th Percentile – Total MOEs are generally in the 71 to 90 range at this percentile, with food significantly contributing throughout the entire year with food MOEs of ca. 100 (Figure III.F.7). MOEs associated with drinking water are generally about 230. Dermal exposures are associated with MOEs of approximately 280 to greater than 2,300.

99.9th Percentile –Total MOEs at this percentile are generally in the 15 to 20 range, with exposure from food dominant throughout the year (Figure III.F.7). MOEs from exposure through the food pathway were in ca. 20. Drinking water exposure resulted in MOEs of approximately 110. Dermal exposures are associated with MOEs of generally ca. 56 to 543.

e. **Children, 1-2 years, Florida Citrus Ground Water**

The results of the total cumulative assessment for Children, 1-2 years using the estimated $BMDL_{10}$ of the index chemical (oxamyl) for the PoD are presented in Appendix II.B.2. Temporal Exposure Profile Plots for Florida Citrus Ground Water appear in Figure III.F.9.

95th Percentile – Total MOEs at the 95th percentile ranged from 67 to 74 (Figure III.F.9). One source of pesticide risk from exposure to pesticides at this percentile of exposure is through the drinking water pathway with total MOEs ranging from 121 to 143. The food component of the assessment was stable across time with an MOE that is generally near 140 across the year.

99th Percentile – At this percentile, the daily MOE values from drinking water sources were ca. 75. Total MOEs averaged about 27. Exposures from oral non-dietary ingestion which are associated with residential use (i.e., hand-to-mouth) were somewhat lower than drinking water exposure and generally the MOEs for oral non-dietary exposure pathway ranged from ca. 290 to greater than 350 (Figure III.F.9). MOEs associated with food were generally around 35. MOEs associated with the dermal pathway are as low as ca. 99.

99.9th Percentile – At the 99.9th percentile, the total cumulative risk (all pathways) generally was in the 6-8 range for this age group and nearly all of the estimated exposure came through the food pathway (Figure III.F.9). Drinking water exposures resulted in MOEs of about 40. Oral non-dietary exposure (hand-to-mouth) resulted in MOEs remaining consistent through the year between 76 and 90. Dermal MOEs generally ranged between ca. 25 and 30.

f. **Children 3-5 years, Florida Citrus Ground Water**

The results of the total cumulative assessment for children, 3-5 years old using the estimated $BMDL_{10}$ of the index chemical (oxamyl) for the PoD are presented in Appendix II.B.2. Temporal

Exposure Profile Plots for Florida Citrus Ground Water appear in Figure III.F.10.

95th Percentile – Total MOEs at this percentile are approximately 95 throughout the year. The significant contributor to total cumulative exposure comes through the drinking water and food pathways (Figure III.F.10) with a MOE of ca. 185 each

99th Percentile – At this percentile, the MOE from food sources generally remained in the 40 range and are essentially equivalent to total (cumulative) exposure since the food pathway predominated. MOEs associated with drinking water were generally near 100. Exposures from oral non-dietary ingestion (i.e., hand-to-mouth) was less than exposure from drinking water and food and MOEs for this source generally ranged from ca. 420 to greater than 480 (Figure III.F.10). MOEs associated with the dermal route appear for the first time here and always exceed ca. 140

99.9th Percentile – At the 99.9th percentile, the total MOE (all pathways) was in the 7 to 10 range for this age group and this was nearly all contributed by food (Figure III.F.10). Dermal is next in importance with MOEs as low as 35. Drinking water MOEs averaged around 60. MOEs varied for exposure through oral non-dietary exposure (hand-to-mouth) around 110. MOEs for dermal exposures generally ranged between 35 and 40.

g. **Adults, 20-49 years, Florida Citrus Ground Water**

The results of the total cumulative assessment for Adults, 20-49 years using the $BMDL_{10}$ for the PoD are presented in Appendix II.B.2. Temporal Exposure Profile Plots for Florida Citrus Ground Water appear in Figure III.F.14.

95th Percentile – Total MOEs at this percentile are in the 420 to 500 range with contributions from drinking water dominant and persistent throughout the year; exposures through the food pathway contribute a relatively small amount compared to total exposure, with MOEs for food above 1300 (Figure III.F.14). Dermal MOEs were all greater than 4,000.

99th Percentile – Total MOEs are generally in the 110 to 160 range at this percentile, with exposure from food and drinking water dominating during the entire year. Drinking water MOEs were consistently about 250. MOEs associated with food are generally

about 260 (Figure III.F.14). Dermal exposures are associated with MOEs of approximately 300 to greater than 2,000.

99.9th Percentile –Total MOEs at this percentile are generally in the 30 to 44 range, with exposure from food which was dominant throughout the year. Drinking water resulted in MOEs of 125 (Figure III.F.14). Dermal exposures are associated with MOEs of generally ca. 50 to greater than 500.

h. **Adults, 50+ years, Florida Citrus Ground Water**

The results of the total cumulative assessment for Adults, 50+ years using the $BMDL_{10}$ for the PoD are presented in Appendix II.B.2. Temporal Exposure Profile Plots for Florida Citrus Ground Water appear in Figure III.F.15.

95th Percentile – Total MOEs at this percentile are ca. 340 with contributions from drinking water all year long of MOEs around 500 and food contributing a relatively small amount of exposure resulting in MOEs above 1000. Dermal MOEs were all greater than 4,000 (Figure III.F.15).

99th Percentile – Total MOEs were generally around 140 at this percentile, with exposure from food dominating during the entire year. MOEs associated with drinking water are generally about 300 (Figure III.F.15). Dermal exposures are associated with MOEs of approximately 330 to greater than 2,000.

99.9th Percentile –Total MOEs at this percentile are generally in the 30 to 40 range, with exposure from food dominant throughout the year (Figure III.F.15). MOEs from exposure through the drinking water pathway were in ca. 160. Dermal exposures are associated with MOEs of generally ca. 80 to 550.

i. **Children, 1-2 years, North Carolina Coastal Plains Ground Water**

The results of the total cumulative assessment for Children, 1-2 years using the estimated $BMDL_{10}$ of the index chemical (oxamyl) for the PoD are presented in Appendix II.B.2. Temporal Exposure Profile Plots for North Carolina Coastal Plain Ground Water appear in Figure III.F.18.

95th Percentile – The significant source of pesticide risk from exposure to pesticides at this percentile of exposure is through the food pathway with total MOEs ranging from 88 to 95 (Figure

III.F.18). The food component of the assessment was stable across time with an MOE that is generally near 140 across the year. Drinking water exposure resulted in MOEs as low as ca. 300. Dermal exposures (associated with residential use) do not occur at this percentile because typically only a small percentage of the population uses such products.

99th Percentile – MOEs associated with food were generally around 35 and comprise the major source for total exposure. Exposures from oral non-dietary ingestion which are associated with residential use (i.e., hand-to-mouth) were somewhat lower than drinking water exposure and generally the MOEs for oral non-dietary exposure pathway ranged from ca. 290 to greater than 350 (Figure III.F.18). At this percentile, the daily MOE values from drinking water sources ranged from 166 to greater than 186. MOEs associated with the dermal pathway are generally greater than 100.

99.9th Percentile – At the 99.9th percentile, the total cumulative risk (all pathways) generally was about 8 for this age group and was nearly all of the estimated exposure came through the oral route comprised mostly of food pathways (Figure III.F.18). Drinking water and oral non-dietary exposure (hand-to-mouth) is next in terms of magnitude of contribution with MOEs from about 70 to 100. Dermal MOEs ranged between 24 and 30.

j. **Children 3-5 years, North Carolina Coastal Plains Ground Water**

The results of the total cumulative assessment for Children, 3-5 years old using the estimated $BMDL_{10}$ of the index chemical (oxamyl) for the PoD are presented in Appendix III.F.19 Temporal Exposure Profile Plots for North Carolina Coastal Plain Ground Water appear in Figure III.F.19.

95th Percentile – Total MOEs at this percentile are approximately 110 to 120 throughout the year. The significant contributor to total cumulative exposure comes through the food pathway (Figure III.F.19) with MOEs of ca. 185. The next most significant contributor to total cumulative exposure is through the drinking water pathway; this pathway has MOEs of greater than 400. Dermal exposures do not occur at this percentile because typically only a small percentage of the population uses such products.

99th Percentile – The total (cumulative) exposure was ca. 35 with most of the exposure through exposure to food. At this percentile, the MOE from food sources generally remained between 39 and

42. The drinking water pathway averaged in MOEs of ca. 250. MOEs for oral non-dietary ingestion (i.e., hand-to-mouth) generally ranged from ca. 420 to greater than 480 (Figure III.F.19). As with Children 1-2 years old dermal exposures do not occur at this percentile.

99.9th Percentile – At the 99.9th percentile, the total MOE (all pathways) was in the 7 to 9 range for this age group and this was nearly all contributed by exposure through the oral route (drinking water, oral non-dietary and food pathways all contributed to these MOEs) (Figure III.F.19). Oral non-dietary exposure (hand-to-mouth) resulted in MOEs generally in the 110 to 120 range throughout the year. MOEs varied for exposure through food around 9. MOEs for dermal exposures were above 30.

k. **Adults, 20-49 years, North Carolina Coastal Plains Ground Water**

The results of the total cumulative assessment for Adults, 20-49 years using the $BMDL_{10}$ for the PoD are presented in Appendix II.B.2. Temporal Exposure Profile Plots for North Carolina Coastal Plain Ground Water appear in Figure III.F.22.

95th Percentile – Total MOEs at this percentile are around 600 with contributions from food a major contributor and persistent throughout the year with MOEs of around 1200; exposures through the drinking water pathway contribute a similar amount compared to total exposure, with MOEs for drinking water above 1100 (Figure III.F.22). Dermal MOEs were all greater than 4,000

99th Percentile – Total MOEs are generally in the 120 to 210 range at this percentile, with exposure from food dominating during the entire year (Figure III.F.22). MOEs associated with food are generally about 230. Drinking water MOEs ranged from ca. 560 to greater than 600. Dermal exposures are associated with MOEs of approximately 280 to greater than 2,300.

99.9th Percentile –Total MOEs at this percentile are generally in the 30-50 range, with exposure from food dominant almost throughout the year (Figure III.F.22). Drinking water MOEs average ca. 300. Dermal exposures are associated with MOEs of generally ca. 50 to 500.

l. **Adults, 50+ years, North Carolina Coastal Plains Ground Water**

The results of the total cumulative assessment for Adults, 50+ years using the $BMDL_{10}$ for the PoD are presented in Appendix II.B.2. Temporal Exposure Profile Plots for North Carolina Coastal Plain Ground Water appear in Figure III.F.23.

95th Percentile – Total MOEs at this percentile are in the 480 to 630 range with contributions from food all year long. Drinking water contributed a relatively similar amount of exposure as food, both resulting in MOEs above 1000. Dermal MOEs were all greater than 4,000 (Figure III.F.23).

99th Percentile – Total MOEs are generally in the 130 to 180 range at this percentile, with exposure from food dominating during the entire year. MOEs associated with drinking water range from 650 to greater than 700 (Figure III.F.23). Dermal exposures are associated with MOEs of approximately 300 to greater than 2,300.

99.9th Percentile –Total MOEs at this percentile are generally in the 40 range, with exposure from food dominant throughout the year (Figure III.F.23). MOEs associated with drinking water range from 300 to greater than 400. Dermal exposures are associated with MOEs of generally ca. 80 to 550

G. Risk Characterization

1. Introduction

Risk characterization is the interpretation phase of the assessment process. This chapter characterizes the risks identified as part of the revised NMC CRA. The intent is to note and discuss uncertainties and strengths in the hazard and exposure elements of risk estimates and to assess quantitatively (when possible) or qualitatively the potential impact of those uncertainties on the risk estimates.

Proper and appropriate risk characterization is particularly important for an assessment as complex as the NMC CRA. Many types of data derived from a variety of sources have been combined to produce estimates of risk from exposure to multiple NMCs in food, drinking water, and from residential use. The outputs of the assessment should be evaluated in a variety of ways. Potential biases in input parameters, the direction of the bias, and the uncertainty surrounding the inputs and the exposure model must be considered with regard to their potential impact on the results of the assessment. Sensitivity analyses are important as is a description of how changes in input assumptions might – or might not—affect the assessment.

This revised NMC CRA reflects the impacts on the risks from implementing the risk mitigation measures from the single chemical assessments. The current document presents the estimates of risks associated with exposures to NMCs in food, drinking water, and from residential uses. For the multi-pathway assessment, food, drinking water, and residential exposures are cumulated as a set of temporal or time-series plots of MOEs over a period of 365 days. Contributions from various pathways and routes of exposure are arrayed separately. The assessment presents and discusses results for the 1-2 year old, 3-5 year old, 20-49 year old, and 50+ year old age groups for the three geographic regions of interest. While the results for infants, 6-12 year old children, 13-19 year old youths, and females 13-49 are not discussed in this chapter, these analyses were performed and are presented in Part III.F of this assessment with the other four age groups.

No single value in the assessment should be used to independently arrive at the interpretation of the results. As discussed below, interpretation of the assessment depends upon the synthesis of a vast body of information about the input data and the processing of that data to determine whether estimated risk is below OPP's level of concern.

2. Hazard and Dose-Response Assessment

The hazard and dose-response assessment is presented in detail in Chapter I.B. That chapter outlines the steps in developing the dose-response relationships for each pesticide based on inhibition of acetylcholinesterase via carbamylation of the active site. It includes a description of all of the data used in the dose-response analyses. Reasons for the selection of oxamyl as the index chemical for the NMC CRA are also discussed. In addition, Chapter I.B describes the dose-time-response model used to develop the dose response curves and half-life to recovery estimates that provided the basis for developing the RPF for each chemical, the PoDs for the index chemical for each route of exposure (i.e., oral, dermal, and inhalation), the FQPA 10X factors, and the inter-species extrapolation factors.

a. **Acetylcholinesterase Inhibition: Data Quality & Common Effect**

The first step in deciding that a cumulative risk assessment was needed was the determination that the NMCs were toxic by a common mechanism, i.e., AChE inhibition via carbamylation of the active site of the enzyme. Once a common mechanism was identified, the next step in the process was to select an appropriate method for combining the risks from exposures to several pesticides from more than one source/route. Data describing the inhibition of AChE in RBCs and brain has been generated for each registered NMC. Studies developed for registration along with studies performed by EPA's NHEERL have been used in this risk assessment. OPP has elected to use the brain AChE data from adult rats as the basis for developing RPFs and PoDs for use in the assessment. Brain AChE inhibition was selected as it reflects a response in a target tissue of concern that is relevant to humans. Although RBC cholinesterase inhibition data do reflect exposure to NMCs and, therefore, the potential for adverse effects, brain AChE inhibition is an indication of direct effects upon the target tissue itself. Error due to the extrapolation between the response in a surrogate tissue (i.e., red blood cell and plasma) and a target tissue itself (brain) is eliminated. In addition, the data for the brain compartment have very narrow confidence limits when compared to those from the blood, suggesting that there is much less variability in this compartment across the data base. As described in Chapter I.B, human studies on RBC ChE are available for aldicarb, oxamyl, and methomyl. EPA has determined, after considering the advice of the HSRB, that these studies are ethically and scientifically acceptable and appropriate for use in this risk assessment. For these three chemicals, inter-species factors were derived by comparing this ChE data from human RBCs with similar RBC ChE data from rats: this comparison was used to replace the standard 10x inter-species uncertainty factor for the three NMC pesticides.

Due to the nature of AChE inhibition with NMCs (i.e., rapid time-to-peak effect followed by recovery), accurate measurements of inhibition can be challenging in the laboratory. The Agency acknowledges this and also the importance of data quality on estimates of potency. As part of the cumulative risk assessment and in an effort to aid in the evaluation of data submitted for registration, ORD performed a series of dose-response studies where data on AChE

inhibition derived from a radiometric method were compared with data derived from a standard Ellman method. When evaluating the toxicity of NMCs, data from the radiometric studies are considered the highest quality. The Agency has also compared results from modified Ellman assays from studies submitted for registration with the radiometric data and has requested and reviewed the SOPs for AChE measurements for NMCs. The review of these SOPs is provided in Appendix II.B.5. Overall, the Agency has concluded that the available database of AChE studies is high quality and appropriate for deriving relative potencies. The Agency is confident that the assessment, as performed, is scientifically and statistically sound and based upon a reliable data set.

A BMD_{10} was selected as the basis for comparison of the dose-response curves for the NMCs. OPP's goal in selecting a point of comparison was to choose a point where the magnitude of the response (cholinesterase inhibition) was reliably distinguishable from background but still be protective of behavioral and functional effects. As described in detail in Chapter I.B, the response level of 10% from control provides this balance. A power analysis has shown that 10% inhibition can be reliably detected in the majority of toxicity studies submitted to EPA. The Agency believes that the BMD_{10} is protective of functional and behavioral effects as none have been observed at levels at or below 10% inhibition.

b. **Dose-Response Analysis**

This assessment uses the RPF approach. Briefly, the RPF approach uses an index chemical as the point of reference for standardizing the common toxicity of the chemical members of the cumulative assessment group. RPFs (i.e., the ratios of the toxic potency of a given chemical to that of the index chemical) are then used to convert exposures of all chemicals in the cumulative assessment group into exposure equivalents of the index chemical. The RPF approach utilizes dose-response information to provide an estimate of each NMC's potency for the common toxicity, and thus allows for the quantification of exposure as it relates to the joint risk of the cumulative assessment group. OPP selected the RPF approach based upon the relatively rich toxicity data base on cholinesterase inhibition available for the NMCs. Although a biological or pharmacokinetic modeling approach would have advantages in determining the cumulative risk for these NMCs, the input parameters for such an approach are not available for most of the NMCs. Thus, OPP has applied simple dose addition and has used an empirical curve fitting model to determine RPFs and PoDs. OPP, in collaboration with ORD, has used an exponential model to describe the dose-time-response curves for each NMC. This dose-time-response model has been used to fit cholinesterase activity data from different studies to derive a BMD in addition to estimation of half-life to recovery. Use of the exponential model to describe cholinesterase data has been subjected to extensive public comment and peer review by the SAP (FIFRA SAP 2001b, 2002, 2005a, 2005b). OPP believes that the model fitting procedure used in this assessment provides reliable estimates of relative potency and PoDs for all routes.

c. **Selecting the Index Chemical**

OPP selected oxamyl as the index chemical for the NMC CRA; this selection was supported by the FIFRA SAP (2005b). Certainty in the PoDs for risk extrapolation is considered to be of great importance in cumulative risk assessment as the PoDs impact the overall uncertainty in the entire risk assessment. Oxamyl has sufficient data for cholinesterase inhibition to support modeling of a BMD_{10} and $BMDL_{10}$ in adult and juvenile rats and human subjects. Moreover, oxamyl studies in adult rats are available for all three routes of exposure (oral, dermal, inhalation) in addition to half-life to recovery in rats and humans. The high quality dose response data for oxamyl permit reliable estimates of PoDs for all routes.

d. **Assumption of Dose-Additivity**

The cumulative risk assessment for the NMCs is based on the assumption of dose-additivity. Dose-additivity is the Agency's assumption when evaluating the joint risk of chemicals that are toxicologically similar and act at the same target site (USEPA, 2001a). The SAP (FIFRA SAP, 2001a) indicated that substantial reliance would have to be placed on what is known about the mechanism of toxicity because it is very difficult to prove dose-additivity at human exposure levels. They further pointed out that studies available on individual chemicals were usually not designed to address the issue of dose-additivity.

Although there are a few interaction studies of *N*-methyl carbamate and OP pesticides in the literature (e.g., Gupta and Dettbarn, 1993; Takahashi *et al.*, 1987), the Agency did not identify any studies conducted using mixtures of more than two *N*-methyl carbamates and which use low dose levels (i.e., that do not produce lethality or profound toxicity). NHEERL scientists have conducted a mixture study using seven *N*-methyl carbamates (carbaryl, carbofuran, formetanate HCl, methiocarb, methomyl, oxamyl, and propoxur) (Padilla et al., 2006). In the mixture study, a dose-additive experimental design was used and the proportion of the NMCs in the mixture was based on their potency using the individual-chemical benchmark dose values as the point of comparison. In general, increasing dosages of the mixture produced increasing decrements in brain ChE activity. Moreover, the dose-additive model predicted the degree of ChE inhibition (RBC and brain) and changes in motor activity within the 95% confidence limits of each predicted value (Padilla et al, 2006; Manuscript in preparation).

The NMCs all act on the same target site– namely, the inhibition of acetylcholinesterase by carbamylation in nerve tissue, which elicits a variety of cholinergic effects. Dose addition is regarded as a reasonable and appropriate approach for estimating the cumulative risk associated with joint exposure to the NMC common mechanism group.

3. Food Assessment

The food component of the NMC cumulative risk assessment is based primarily upon two extensive, reliable data sets: 1) USDA's Continuing Survey of Food Intakes by Individuals, 1994-1996 and 1998 (CSFII) and 2) USDA's Pesticide Data Program (PDP). The CSFII provides a detailed representation of the food consumption patterns of the U.S. public across all age groups, during all times of the year, and across the U.S. The PDP data provide a very reliable sample of pesticide residues in the major children's foods, including fruits, vegetables, milk, grains and beef/poultry/pork. The PDP program utilizes multi-residue analytical methods such that co-occurrence of several pesticides in individual samples is captured, alleviating much of the uncertainty that otherwise might exist about co-occurrence in foods that are monitored in the program. These two sources of data – CSFII consumption data and PDP petisticide residue data -- provide a firm foundation upon which to assemble other data to develop the NMC cumulative risk assessment and are discussed in more detail below.

a. Consumption Data

As with the previous cumulative risk assessments performed by OPP, this revised NMC assessment is based on dietary consumption data obtained from the USDA's CSFII 1994-96/98. This is an extensive, two-phase (1994-1996, and then 1998) survey and includes more than 20,000 individuals sampled over four years. The CSFII 1998 provided an additional 5,559 consumption diaries for children ages newborn through nine years of age, which supplemented the 4,253 children sampled in the CSFII 1994-96. This additional, supplemental children's survey was specifically requested of USDA by OPP in order to improve the means to assess exposures to children. In each year of the survey, approximately 5,500 participants in 62 geographical areas across the country were interviewed on their dietary consumption over two separate (non-consecutive) days. The survey was designed to provide a nationally representative sample of non-institutionalized persons residing in the U.S. USDA also provides sampling weights, which allow the survey results to be projected to the U.S. population.

The sampling procedure was designed to account for inter-individual variability in individual consumption patterns (e.g., types and amounts of foods eaten) due to differences in age, gender, ethnicity, regional location, and socioeconomic status. Also, survey respondents are interviewed on different days of the week throughout the year to

account for seasonal and within week variability in consumption patterns. A number of other aspects of the survey are also controlled in order to maximize the prospect that the results are representative not only of the entire U.S. population, but also particular subgroups, including those for which OPP generates acute dietary food exposure distributions.

While the USDA food consumption surveys are designed to be generally representative of the U.S. population, it is clear that some factors that can influence dietary choices are not addressed in the survey design. For example, the CSFII surveys do not purport to be representative of people in institutional living arrangements (colleges, nursing homes, etc.) or of different religions or health status. Specific subpopulations such as vegetarians, those on restricted diets, or those on specialized diets were not specifically surveyed. In addition, smaller specialized subpopulations such as Native Americans or subsistence fishermen are not specifically targeted[p]. Overall, however, the dietary information which OPP used for the cumulative assessment of NMC pesticides is the highest quality data available and is representative of many subgroups in the U.S. population. The consumption data available from the CSFII 1994-96/1998 provide a reasonable basis for estimating NMC food exposure for the subpopulations surveyed.

b. **PDP Monitoring Data in the Assessment**

USDA PDP data are used for all of the measured pesticide residues in the revised NMC CRA. PDP samples fruits, vegetables, juices, meats, grains, and dairy products at central distribution centers and warehouses immediately prior to distribution to supermarkets or grocery stores. The samples are washed and inedible portions (e.g., cores, peels, etc.) are removed prior to analysis. PDP data, thus, closely reflect residues in foods, as consumed. OPP has applied factors, where available, to the PDP data to account for cooking and processing that might further reduce residues (e.g., cooked potatoes, canned beans). Thus, pesticide residue data used directly from PDP or adjusted with processing factors accurately represent pesticide concentrations to which consumers are exposed.

The use of PDP as a source of residue data has a number of inherent benefits that minimize the need to incorporate conservative assumptions in the assessment and produces more realistic exposure estimates. The PDP sampling design and procedures provide OPP with a nationally representative sample of selected food commodities available to the U.S. population in grocery stores. OPP assumes a uniform distribution of these food commodities across the U.S. While the assumption of nationally uniform distribution of foods does not reflect highly localized

[p] Although populations that rely primarily on fish consumption were not specifically targeted in CSFII, available residue data indicate that fish consumption is not a major source of pesticide exposure for currently registered pesticides in general, nor NMCs in particular.

consumption events that may be occur as a result of individuals obtaining foods at road side stands or local farmers markets and consuming it closer to the time of harvest than the foods available in larger grocery stores, it is believed that only a small percentage of food consumed is actually obtained from these sources and would be affected by this assumption. In addition, as noted above, PDP uses multi-residue methods and so provides a direct measure of the co-occurrence of multiple pesticides in each sample analyzed. Thus, the PDP data inherently reflect existing use patterns of pesticides. Given the size, scope, quality, and breadth of the PDP sampling program, these data provide the best available information regarding pesticide residues in the U.S. food supply.

c. **Data Translation from PDP**

Not all food commodities treated with NMC pesticides are monitored in PDP. OPP has developed a procedure by which commodities that are sampled by PDP serve as surrogate data sources for some commodities that are not. This approach is outlined in OPP/HED SOP 99.3 (USEPA, 1999b). It is based upon the concept that families of commodities with similar cultural practices and insect pests are likely to have similar insecticide use patterns. Although this approach is generally sound, it introduces uncertainty with regard to how similar the use patterns for a given pesticide are to those for even closely related commodities.

For example, the same pesticide may be applied to several crops belonging to the same crop group (or family) on a similar time schedule. However, the application rates and/or the number of treatments may differ between the treated crops. Such issues should be taken into consideration when conducting sensitivity analyses of the results of the risk assessment. When such translations are done in a cumulative risk assessment, the assumption of similar agricultural practices is inherently applied to all the pesticides in the cumulative assessment group and the co-occurrence of pesticides on the surrogate commodity is extended to the commodities to which the residues are being translated if the translated commodity is a registered use. Whether any such potentially inappropriate translations overestimate or underestimate exposure will differ from one commodity to another. However, the impact of any such potential translation errors on total exposure is not likely to be significant since the commodities for which PDP data were translated represent less than 1% of the mean per capita consumption by small children.

d. **Other Sources of Residue Data**

The PDP program provides pesticide residue data for a variety of fruits, vegetables, juices, meats, grains, and dairy products. Never-the-less, PDP data -- and its associated surrogate data for translated commodities -- still do not cover all food commodities of interest. For example, PDP does not currently include data for seafood and eggs; for these

commodities, FDA's Total Diet Study and FDA Monitoring data were reviewed. No NMC residues were found in seafood or eggs in either of these programs. Thus, the analytical results suggest that eggs and seafood contain negligible residues of NMCs and OPP used a zero to represent NMC pesticide concentrations in these commodities. OPP considers this factor neutral with regard to the impact on the results of the assessment.

Approximately 3% of the foods consumed by children 1-2 years of age still remains unaccounted for after considering the PDP data, the FDA Total Diet Study data, and the FDA surveillance monitoring data. This includes sugar, molasses, and various oils and syrups which were assigned a residue value of zero. Evidence suggests that these commodities would have *de minimis* pesticide residues. These products are highly processed commodities that are unlikely to retain any significant residues following the intensive commercial processing they undergo. PDP has sampled high fructose corn syrup during 1998 and 1999 and did not find residues of any pesticide. PDP has also sampled field corn during the 2006-2007 period and only found one sample containing an NMC pesticide (carbaryl) at a very low (ppb) concentration. The limited data from the Total Diet Study found no residues in pancake syrup or sugar. OPP believes that the assumption of zero residues for highly processed commodities such as those described above will not result in a significant under-estimation of exposure to NMC pesticides from food for children or any other subpopulation.

No data are available for commodities such as dried beans, spices, seeds, nuts, and low consumption specialty crops (such as avocado, kiwi, raspberry, and mango). OPP believes that the omission of various low consumption and specialty foods from the assessment will not significantly under-estimate exposure to NMC pesticides from food for children or any other subpopulation.

e. **Impact of Regulatory Actions**

There has been significant mititgation measures implemented on many NMCs as a result of the individual chemical decisions, including canceling uses, lengthening pre-harvest intervals, and reducing the number and/or application rates. As a result, during the period since the issuance of the preliminary NMC CRA in August 2005, the Agency has identified, and in some cases imposed, risk reduction measures on some of the major contributors to carbamate cumulative risk, as discussed below. The risk estimates presented in the revised NMC CRA reflect the risk mitigation measures identified for or taken on individual carbamates since FQPA was signed into law in August 1996. A table summarizing these mitigation measures is provided in Appendix II.A. These mitigation measures generally reflect determinations of risk based on EPA's assessment of the single chemical's risks. For all of the risk mitigation measures that are reflected in this document, EPA has either commenced the processes necessary to implement its selected risk

mitigation or intends to commence the appropriate processes in the near future. Having already determined that the identified risk mitigation is warranted for the individual chemical regardless of the cumulative assessment, EPA has chosen to reflect that mitigation in this assessment, and consequently has excluded uses that are slated for cancellation from this assessment.[q] More specifically: in cases for which agreements have been signed or voluntary cancellations are being implemented or have been requested by the pesticide registrant, the uses have been excluded from the assessment. Examples include use of methomyl on strawberries and grapes. In addition, EPA has excluded all uses where specific mitigation measures such as cancellation have been identified and proposed based on single-chemical risk assessments. For example, EPA has excluded all carbofuran uses from the cumulative assessment except the few import tolerances that the Agency is not proposing to revoke. (See Chapter I.A for additional details regarding the specific cancellation actions that have taken place.)

For other pesticides, pre-harvest intervals have been extended or application rates have been reduced. For example, pesticide use labels for commodities such as apples, peaches, pears, potatoes, nectarines, oranges, and strawberries were modified at various times in the past several years to reduce residues of a number of NMCs such as aldicarb, carbaryl, and formetanate HCl. To reflect the impact of these risk mitigation measures, EPA used residue data only from years after the measures had been implemented (i.e. the more recent years that reflect the changes in pesticide use practices). PDP data from prior years – that reflect older, discontinued use patterns – were not included. To the extent that the impacts of risk mitigation measures on residue level are not yet apparent in the available PDP monitoring data, the PDP residue data will not reflect the expected decrease in exposure and the assessment likely overestimates risk on this basis.

f. Impact of Assumptions: Sensitivity Analyses

The following section describes sensitivity analyses conducted on the cumulative food assessment. These analyses focus on four areas:

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[q] As a practical matter, EPA determined that it would serve no purpose to include such uses in the cumulative assessment. Other than by adding a new issue that might delay action, adding these uses would not likely have any impact on the timing or substance of any cancellation decision relating to such uses. Given that the purpose of tolerance reassessment is to determine whether regulatory action should be initiated to modify or revoke tolerances that the Agency finds do not meet the safety standard of section 408, there seems to be little value in including uses in the assessment that will disappear regardless of their impact on cumulative risk; the critical issue for determining whether regulatory action will have to be initiated under section 408 is whether the uses that will remain result in unacceptable dietary risk. EPA recognizes, however, that to the extent that any risk mitigation measures are not subsequently implemented as envisioned in this assessment, the N-methyl Carbamate cumulative assessment will have to be revised as necessary.

- Limit of detection in PDP and the use of 'zero' assumption for non-detectable residues;
- Comparison of exposure estimates using all available PDP data deemed appropriate for the CRA with those using only the PDP data from recent years;

- Summation of exposure over 24 hours instead of smaller time increments or individual eating events that would better account for rapid reversibility on NMCs; and

- Consideration of a chemical-specific adjustment factor approach for the inter-species extrapolation factor

Each of these sensitivity analyses is discussed below.

i. Limit of Detection in PDP: Use of 'zero' assumption for non-detectable residues

One of the important attributes of a cumulative risk assessment is that its scope and complexity, unless carefully considered, can potentially lead to inflated estimates of risk due to compounding conservatisms which would reduce the interpretability and ultimately the utility of the assessments. When little or no information is available to inform potential sources of exposure, a single chemical assessment may incorporate conservative assumptions to reflect reasonable worst case exposure estimates. In cumulative risk assessments, the incorporation of such conservative assumptions would imply multiple *simultaneous* reasonable worst case exposure estimates for each individual chemical. As such, some of the conservative assumptions appropriately used in the single chemical risk assessments are not appropriate or reasonable for use in a cumulative risk assessment.

One example is the way in which assumptions for single chemical versus cumulative (multiple) chemical assessments differ for PDP samples with no detectable residues. For any analytical method, there is a minimum concentration at which a compound must be present in order for it to be reliably detected in the sample. This minimum level is referred to as the analytical method's limit of detection (LOD). With respect to a specific pesticide, a sample having no detectable residue (i.e. a residue below the LOD) is referred to as a non-detect. A non-detect does not necessarily imply that no residues are present; instead, a non-detect simply indicates that residues, if present, are present at concentrations less than the LOD. In single chemical assessments, certain non-detects are assumed to be present at one-half the LOD of the analytical method (more specifically: those non-detects for which percent crop

treated information suggests were actually treated with the pesticide of interest). In contrast, *all* PDP samples with non-detectable residues are assumed to be "zero" for this and other cumulative risk assessments. Although the result of replacing all non-detectable residues with "zero" values might intuitively suggest a bias toward under-estimation of risk, OPP has conducted a sensitivity analysis and determined that this assumption has little impact on the upper end of the exposure distribution for the NMCs covered by this assessment and upon which EPA has based its regulatory decisions. The most highly exposed individuals tend to be associated with relatively high consumption of high residue values, not residues below PDP's limits of detections. The details of this sensitivity analysis are provided below.

The sensitivity analysis is presented in Table I.G-1 and indicates that assuming residues of one-half LOD for all non-detects of the most frequently detected NMC pesticide on each commodity increased the estimated exposure by 4.2% for both groups of children ages 1-2 and 3-5 years at the 99.9th percentile.

Table I.[STYLEREF 2 \s]-[SEQ Table * ARABIC \s 2]. Sensitivity Analyses for NMC Cumulative Food Assessment: Limit of Detection Assumption[a]

Age Group		Estimated Exposure at the 99.9th Percentile (mg/kg oxamyl equivalents)	MOE at the 99.9th Percentile	Percentile at which Target of 10 is Reached
Baseline CRA	Children 1-2	0.0229	7.9	99.848th
	Children 3-5	0.0209	8.6	99.870th
LOD of PDP: Replace 0s with one-half LOD	Children 1-2	0.0238	7.6	99.833th
	Children 3-5	0.0217	8.3	99.859th

[a] The sensitivity analyses performed here in the CRA with the LOD differ from those that are typically performed for LOD values in the single chemical assessments in two ways: (1) rather than assuming that every chemical in the assessment group is present on the non-detect samples, only the most frequently detected chemical on each commodity is assumed to be present at one-half the LOD. The rationale behind this approach is that the most

commonly detected pesticide on each commodity is likely to be the most widely used pesticide on that particular commodity and thus most likely to be present at level lower than the PDP LOD; and (2) in contrast to single chemical assessments for which only treated commodities are assigned one-half LOD values, all non-detect samples of a particular commodity are given a value of one-half the LOD rather than only some of the non-detects in the cumulative assessment.

As can be seen from the baseline analysis using zero residues for all PDP non-detect data, the calculated MOEs at the 99.9th percentile of exposure are 7.9 and 8.6 for children 1-2 and 3-5, respectively, with MOEs reaching the target of 10 at the 99.848th and 99.870th percentiles of exposures[r], respectively. After replacing the zero values with one-half LOD values in the manner described above, the calculated MOEs at the 99.9th percentile of exposure decrease to 7.6 and 8.3 for children ages 1-2 and 3-5 years, respectively, with MOEs reaching the target of 10 at the 99.833th and 99.859th percentiles of exposures, respectively. This indicates that the use of zero for PDP non-detect data has only a minimal effect on estimated high-end exposures. The results of this sensitivity analysis are not unexpected: generally, the LODs for PDP data are very low (the average LOD for the entire data base is about 0.01 ppm) and the vast majority of exposures at the upper percentiles are derived from detectable residues in a single commodity rather than from multiple commodities having one-half LOD residue values. Therefore, it seems reasonable that the effect of assumptions related to estimation of values below the LOD would not significantly influence exposure estimates at the highest percentiles of exposure and this sensitivity analysis has demonstrated that the manner in which non-detects are handled in the dietary assessment does not significantly impact exposure estimates of the most highly exposed children.

ii. Use of Recent PDP Data Only

As described above, PDP data provide a critical component of the cumulative food risk assessment as this database provides reliable residue data for commonly consumed commodities sampled near their point of sale. As such, the PDP data provide a realistic estimate of pesticide residues actually consumed by the public. Except in cases where the Agency has mitigated exposures through modification of pesticide labels, has cancelled uses, and/or has revoked tolerances, essentially all available PDP data (1994-2006) have been used in the revised NMC CRA.[s] The practice of incorporating all available PDP data is consistent with previous preliminary, revised, and updated cumulative risk assessments conducted by the Agency, including the OP CRA (USEPA, 2006a). Use of all relevant data takes

[r] In this table --and all subsequent tables which provide summary information regarding the Agency's sensitivity analyses -- EPA has elected to express exposures to three significant digits and percentiles at which the target MOE of 10 is reached to 5 digits. The Agency fully recognizes that its exposure assessment tools are insufficient to produce this level of precision, but has chosen to display the results of its sensitivity analysis to this level in order to more effectively illustrate the changes that occur in the CRA when assumptions or other input parameters are modified. The reader should note that any perceived differences in exposure or risk at this level are well beyond the ability of the Agency to measure or detect.

[s] For reasons described in the food chapter, PDP data from 1992 and 1993 were not used.

advantage of more samples, and thus more data, for use in the Monte Carlo simulations. Moreover, incorporation of a wide range of years of PDP data may better capture the typical and ever-present transient shifts in pesticide use practices due to temporal variations in weather and/or pest pressures. Any of these changes may ultimately result in higher or lower pesticide residues or an increased or decreased frequency of residues found in food. On the other hand, it is possible that PDP data that are older than five years may not best represent current agricultural practices and expected dietary exposures. For example, changes in the pesticide market resulting in less expensive or more effective alternatives and/or gradual decline or shifts in use due to pesticide resistance may make older PDP pesticide data less representative of current and (expected) future conditions than more recent data (e.g., within 5 years).

To evaluate the degree to which changes in pesticide use practices over time may or may not have affected the estimated exposures and risks, OPP performed a sensitivity analysis in which only the most recent PDP data (2002-2006) were used. Specifically, OPP ran a second, supplemental analysis which used only the last five years of PDP data (except for a few commodities like frozen green beans, grape juice, and fresh cherries that were not sampled in any year from 2002 to 2006) instead of using all PDP data (1994-2006) that defines the baseline. The purpose of this analysis was to determine if the elimination of earlier (pre-2002) PDP data -- which might be considered less typical of current use patterns and practices -- would significantly affect the exposure and risk estimates. The details and results of this sensitivity analysis are provided in [REF _Ref178101107 \h].

Table I.[STYLEREF 2 \s]-[SEQ Table * ARABIC \s 2]. Sensitivity Analyses NMC Cumulative Food Assessment: Recent PDP Data Assumption

Age Group		Estimated Exposure at the 99.9th Percentile (mg/kg oxamyl equivalents)	MOE at the 99.9th Percentile	Percentile at which Target of 10 is Reached
Baseline CRA	Children 1-2	0.0229	7.9	99.848th
	Children 3-5	0.0209	8.6	99.870th
Recent PDP Data Only	Children 1-2	0.0185	9.8	99.895th
	Children 3-5	0.0170	10.6	N/A

As can be seen in this table, the calculated MOEs at the 99.9th percentile of exposure are 7.9 and 8.6 for children ages 1-2 and 3-5 years, respectively, using all relevant PDP data (1994-2006). MOEs reach the target of 10 at the 99.848th and 99.870th percentiles of exposures for children ages 1-2 and 3-5 years, respectively. When using only the most recent PDP data (2002-2006), the calculated MOEs at the 99.9th percentile of exposure are 9.8 and 10.6 for children ages 1-2 and 3-5 years, respectively, with the MOE for children 1-2 reaching the

target of 10 at the 99.895th percentile of exposure. The results of this sensitivity analysis suggests that EPA has not significantly underestimated – and may have overestimated -- exposures by using all years of PDP instead of only the most recent years. To the extent that the most recent years of PDP data are more representative of present and future-expected exposures, an MOE of 10 was reached at the 99.895th percentile for children 1-2 and were greater than 10 for children 3-5.

iii. Summing food exposures over 24 hours

Another key principle in cumulative risk assessment is the proper matching of duration of the toxic effect (What is the time to peak effect? What is the time to recovery?) and the duration of exposure (When do exposures occur? How long or how often do exposures last? Do exposures overlap?). As described in Chapter I.B, the nature of NMC toxicity is rapid onset (typically 30 min to 1 hour) followed by rapid recovery (one-half life to recovery is typically approx. 2 hours). Conceptually, a robust multi-chemical, multi-pathway PBPK or PBPK/PD model would be ideal to account for the timing of environmental exposure(s) and the timing for AChE inhibition and recovery. However, at this time, such a model is not available. In lieu of such a model, EPA has used the RPF method to quantify chemical potency. In this assessment, each NMC was converted into units of the index chemical, oxamyl. The probabilistic exposure models (DEEM-Calendex, Lifeline, SHEDS) used in this assessment sum exposures to oxamyl equivalents over 24 hour periods. These models do not allow the typical user to separate exposures into time steps smaller than 24 hours or to separate exposures by exposure events (i.e., breakfast, lunch). Due to the rapid recovery associated with NMC toxicity, 24 hour exposure periods may or may not, *a priori*, be appropriate. More specifically, to the extent that a day's eating occasions leading to high total daily exposure are close together in time or occur from a single eating event, the approach used in this revised assessment which sums eating events over a 24 hour period provides reasonable estimates of risk from food. Under this assumption, minimal AChE recovery would occur between eating occasions (i.e., exposure events) since exposure events are assumed to occur close together. Conversely, if eating occasions leading to high total daily exposures are widely separated in time (within one day), then substantial AChE recovery would occur between eating occasions and the estimated risks in the cumulative risk assessment could be overstated.

In the absence of a fully developed PBPK model and in the absence of probabilistic exposure models that can evaluate exposure durations shorter than 24 hours, OPP began an examination of the exposure patterns for food records from the high end of exposure distribution with the case study presented to the SAP in February, 2005 and followed this work in a presentation of the preliminary NMC CRA to the SAP in August 2005. OPP acknowledged this aspect of the limitations in the currently available probabilistic food exposure models and these early exercises were an attempt at determining the degree to which high-end food exposures in the NMC CRA could be attributed to specific

eating occasions (within a day) that may (i) occur closely spaced in time, (ii) occur widely separated by time, or (iii) come from single eating events. This was done by looking at actual individual eating occasions as recorded in the USDA's CSFII. The records in the CSFII capture detailed information not only about the identity and amount of foods consumed, but also about the timing of each eating occasion within a 24-hour period; it was these consumption diary records that were examined for those survey respondents at the upper end (99.8^{th} to 100^{th} percentile) of the exposure distribution. To the extent that a day's eating occasions leading to high total daily exposure might be found close together in time or to occur from a single eating event such that minimal AChE recovery occurs between eating occasions (i.e., exposure events), the "24 hour sum" approach, which sums eating events over a 24-hour period, would provide reasonable estimates of risk from food. To the extent that eating occasions leading to high total daily exposures are widely separated in time such that substantial AChE recovery occurs between eating occasions, the estimated risks under any 24 hour sum approach may be overstated and a more sophisticated approach – one that accounts for intra-day eating patterns and the recovery of AChE between exposure events -- may be more appropriate.

The updated analyses described here as part of this revised NMC confirms EPA's prior analysis that daily exposures to NMC pesticides in the upper extremes of the distribution (99.8+ percentile) for exposures from food mainly involve single eating events. Specifically, OPP found that a large fraction (~80%) of daily records for children 1-2 and children 3-5 years old contributing to the upper tail of the food exposure distribution represent single eating occasions. Less than about 3% of these upper-end diary records result from exposures that are divided among three or more eating occasions. (Figures I.G-1& I.G-2).

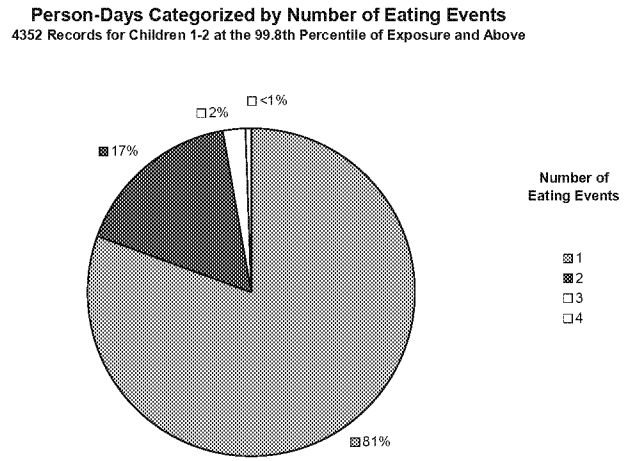

Figure I.[STYLEREF 2 \s]-[SEQ Figure * ARABIC \s 2]. Number of Eating Events Contributing to Exposures at 99.8+ Percentile for Children 1-2

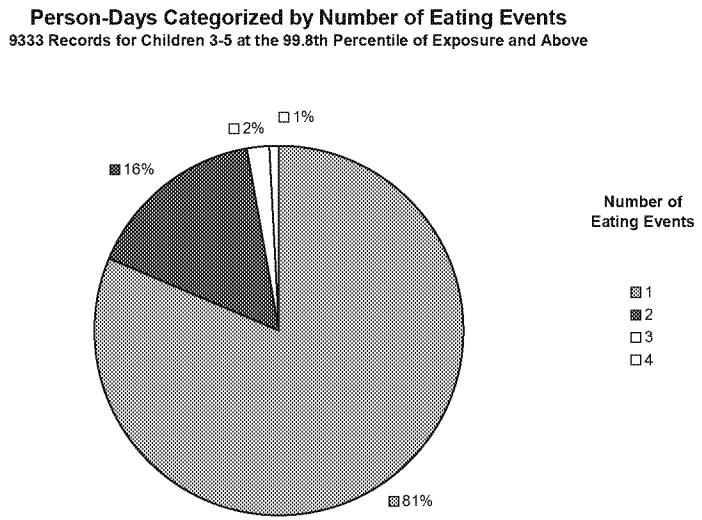

Figure I.[STYLEREF 2 \s]-[SEQ Figure * ARABIC \s 2]. Number of Eating Events Contributing to Exposures at 99.8+ Percentile for Children 3-5

These pie charts represent exposures from the 99.8th to 100th percentile of exposure distribution, use PDP data through 2006, and exclude eating events that contribute small amounts (<10%) of total daily exposure. Similar pie charts representing PDP data through 2004 were presented to the SAP in February 2005 as part of the NMC Case Study and August 2005 as part of the preliminary NMC CRA. At these SAP meetings, EPA concluded and the SAP agreed that since most food exposure to NMCs occurred in a single eating event, a more sophisticated, temporal-based approach which evaluated food exposure patterns throughout the day was not warranted.

As part of the risk characterization phase of this revised NMC CRA, the Agency has further refined its assessment of within-day consumption of food and used a second approach to characterizing the effect of eating occasions with respect to the timing of exposure events. In this second approach, OPP worked collaboratively with ORD's National Exposure Research Laboratory (NERL) to use the SHEDS (Stochasistic Human Exposure Dose Simulation) model to evaluate the impact of rapid AChE recovery on estimates of food exposure. Specifically, the ORD SHEDS model was used to bound the maximum extent to which accounting for NMC reversibility could potentially reduce estimates of exposure. The SHEDS model provides the user with greater ability to perform "what if" analysis, particularly with respect

to dietary consumption data which is hard-coded in DEEM and the other dietary exposure models. This greater ability to specify the use of specific dietary records affords the risk assessor the ability to select specific eating occasions to include in the assessment. With respect to investigating the effect of NMC half-lives on exposure estimates, this capability permitted the Agency to exclude -- from each individual CSFII food consumption record -- all eating events resulting in NMC exposures *except the eating event resulting in the largest exposure to each individual*. Here, all other eating events were assumed to result in zero exposure and only the eating event associated with each individual's maximum exposure was retained. This is equivalent to assuming an infinitesimal half-life for all NMCs (i.e., complete and instantaneous recovery) and provides a bounding estimate that demonstrates the maximum theoretical effect that quantitative incorporation of half-lives could have on exposure estimates. The results of this bounding exercise are shown below in Table I.G-3.

Age Group		Estimated Exposure at the 99.9th Percentile (mg/kg oxamyl equivalents)	MOE at the 99.9th Percentile	Percentile at which Target of 10 is Reached
Baseline CRA	Children 1-2	0.0229	7.9	99.848th
	Children 3-5	0.0209	8.6	99.870th
Summing Exposure over 24 Hours	Children 1-2	80% of individuals at the 99.8th percentile of exposure and above were due to exposures from one eating event		
	Children 3-5			
	Children 1-2	0.0220	8.2	99.86th a
	Children 3-5	0.0196	9.2	99.88th a

[a] These percentiles are reported to only four significant digits: these are produced by the ORD SHEDS model and only reported to two decimal places

This bounding exercise reduces exposure at the 99.9th percentile by no more than about 3-9% depending on age group. For 1-2 and 3-5 year old children, exposure estimates are reduced by 6% and 7%, respectively. MOEs would be expected to change in a similar (proportionate) manner.

As described above, two approaches have been used to evaluate the extent to which the Agency's 24-hour approach to food risk assessment overestimates risk from the NMCs. The results of both approaches indicate that the cumulative risk to NMCs is indeed not substantively overestimated using the current exposure models and the 24-hour approach. This is due to the fact that exposure to NMCs occurs predominantly through single eating events and not from multiple events that occur throughout the day. Based on these analyses, the Agency concludes that the current exposure assessment methods used in the revised NMC CRA provide realistic and high confidence estimates of risk to the NMCs through food.

iv. Consideration of Chemical Specific Adjustment Factor Approach for the Inter-species Uncertainty Factor

The Agency has applied a 10X factor for inter-species extrapolation in the NMC cumulative risk assessment for those NMCs without human studies. This 10X factor is consistent with typical Agency practice for most single chemical and cumulative risk assessments. The following text describes a sensitivity analysis employing an alternative approach used by the WHO for performing inter-species extrapolation.

In 2005, the WHO published its guidance for deriving chemical specific adjustment factors (CSAFs) (WHO, 2005). This CSAF guidance describes approaches for use of kinetic and mechanistic data to refine inter-species and intra-species extrapolation factors. The International Programme on Chemical Safety (IPSC) guidance is based in large part on analyses by Renwick (1993) and Renwick and Lazarus (1998) which describe the use of toxicokinetic and toxicodynamic data as a means of replacing the traditional 10-fold safety factors for human sensitivity and animal-to-human extrapolation. Although EPA does not yet have guidance for developing CSAFs, the Agency has used these concepts in a few risk assessments. One such example includes the recent risk assessment for dimethyl arsenic acid (DMA) where the available *in vivo* and *in vitro* mode of action and metabolism data supported toxicodynamic equivalence between rats and humans and thus the inter-species factor was reduced to 3X for DMA.

Understanding mode of action is an important component of deriving CSAFs in that it provides the foundation for understanding what toxicokinetic and/or toxicodynamic characteristics are critical for evaluating inter- or intra-species extrapolation. In the case of NMCs, the mode of action is well understood in both animals and humans. Specifically, in rodents and humans, NMCs cause neurotoxicity via the inhibition of AChE by carbamylation of the serine hydroxyl group located in the active site of the enzyme leading to accumulation of acetylcholine and ultimately clinical signs. As part of the risk characterization for the revised NMC CRA, the Agency has considered the extent to which available data support a CSAF-type approach for those NMCs without human toxicity studies. Regarding toxicokinetics, unlike many OPs, NMCs do not require activation; the parent compound is an active AChE inhibitor. Although some metabolites of NMCs have been shown to be active AChE inhibitiors, none have been shown to be more potent than the parent active ingredient. Thus, metabolism is considered to be a detoxification process. As such, species differences in tissue dosimetry are likely correlated with differences in body weight to the ¾ power and are also consistent with a 3X factor to account for inter-species differences in toxicokinetics (USEPA, 2006).

Regarding toxicodynamic characteristics, as noted above, the mode of action of NMCs is applicable to animals and humans such that inhibition of AChE leads to clinical signs of neurotoxicity. The AChE enzyme in humans and rats has similar function and structure. (See reviews by Radic and Taylor, 2006 and Sultatos, 2006.) The half-life to recovery values for rats and humans provided in Table I.B-9 range from approximately 1 to 2 hours and demonstrate the similarity of the half-lives of the two species. Based on this information, given a similar dose or concentration at the target site, it is likely that human and rat AChE would respond similarly. It may be possible to use *in vitro* studies using human and rat tissues and human and rat AChE to test this hypothesis. In other words, it may be possible to use *in vitro* studies to demonstrate toxicodynamic equivalence between rats and humans. If these data were available and they showed toxicodynamic equivalence, the Agency could reduce the inter-species factor for those NMCs without human toxicity studies to 3X. Because of the lack of these *in vitro* studies, the Agency does not believe it appropriate at this time to

further refine the standard 10X factor for inter-species extrapolation. Instead, the Agency has used the CSAF approach as a sensitivity analysis in its risk characterization.

The Agency also notes that *in vivo* studies with human subjects are available for three NMCs (aldicarb, oxamyl, methomyl). These studies were determined by EPA, after considering the advice of the Human Studies Review Board, to be ethically and scientifically acceptable for use in this risk assessment. The Agency has developed BMD estimates in rats and humans for RBC AChE inhibition. This analysis has shown that the ratio of the BMDs for rat/human ranges from 2 to 5 for these NMCs. This range would tend to support the CSAF approach described here to reduce the standard 10X inter-species factor to 3X as part of the sensitivity analysis in the risk characterization for those NMCs without human data and which make meaningful contributions to the cumulative risk.

In this sensitivity analysis, the 10X inter-species factor was reduced to 3X based on the assumption of toxicodynamic equivalence for carbaryl, carbofuran, and formetanate HCl. These three NMCs were selected as they contribute to the overall cumulative MOEs. The results of this sensitivity analysis are shown below in [REF _Ref178101703 \h].

Table I.[STYLEREF 2 \s]-[SEQ Table * ARABIC \s 2]. Sensitivity Analyses NMC Cumulative Food Assessment: CSAF Approach for Inter-species UF

Age Group		Estimated Exposure at the 99.9th Percentile (mg/kg oxamyl equivalents)	MOE at the 99.9th Percentile	Percentile at which Target of 10 is Reached
Baseline CRA	Children 1-2	0.0229	7.9	99.848th
	Children 3-5	0.0209	8.6	99.870th
CSAF Approach for Inter-species UF	Children 1-2	0.0183	9.8	99.896th
	Children 3-5	0.0171	10.5	N/A

10X inter- Using the standard species factor for all NMCs without human data, the (baseline) MOEs at the 99.9th percentile of exposure reach the target of 10 at the 99.848th and 99.870th percentiles of exposures for children 1-2 and 3-5 years, respectively as shown in Table I.G-4. However, when considering an alternative approach to the inter-species factor which assumes a 3X inter-species factor for carbaryl, carbofuran, and formetanate HCl, the MOEs at 99.9th percentile of exposure increase to 9.8 and 10.5 for children 1-2 and 3-5 years, respectively, with the exposure for

the younger age group reaching the target MOE of 10 at the 99.896th percentile of exposures. [Note: because of the lack of key *in vitro* studies to confirm the assumption of toxicodynamic equivalence, the Agency did not believe it appropriate at this time to use a 3X factor for inter-species extrapolation in the baseline assessment. Instead, the Agency has used the CSAF approach as a sensitivity analysis in its risk characterization.]

g. **Model Outputs & Discussion**

The food component of the NMC cumulative risk assessment was conducted using the DEEM software. This software program evaluates the full range of dietary exposures and permits a detailed evaluation of the source of exposures with regard to which foods and pesticides are the predominant sources of the exposure. The results of the food portion of the revised NMC cumulative risk assessment using baseline assumptions as wel as the various sensitivity analyses are summarized in Tables I.G-1 through 4 with detailed discussion of methods and approaches presented in Chapters I.C and I.G.

Table I.G-5 below presents a summary of the NMC Cumulative food assessment baseline MOE estimates and the percentiles at which the target MOE of 10 is reached.

Table I.[STYLEREF 2 \s]-[SEQ Table * ARABIC \s 2]. Summary of NMC Cumulative Food Assessment: Baseline Estimates

Age Group	Percentiles of Exposure	MOE at the Selected Percentiles	Percentile at which Target of 10 is Reached
Baseline cumulative risk assessment			
Children 1-2	95	141	99.848th
	99	35	
	99.9	7.9	
Children 3-5	95	185	99.870th
	99	40	
	99.9	8.6	
Adults 20-49	95	1278	N/A
	99	236	
	99.9	42	
Adults 50+	95	1035	N/A
	99	193	

	99.9	40	

The results are presented in the form of MOEs for children 1-2 and 3-5 years of age and for adults 20-49 and 50+ years of age. MOEs at the 95th, 99th, 99.5th, and 99.9th percentiles of exposure are presented for each age group. Children 1-2 and 3-5 years old are consistently the most highly exposed subgroups in the analysis.

Due to the complex nature of cumulative risk assessments, it is important not to use any single point or any MOE estimate alone or in isolation. Each estimated MOE is derived from a combination of data from multiple sources that describe multiple areas of exposure or hazard. Each dataset and assumption used to derive the MOEs includes its own variability and uncertainty. Moreover, some datasets contain more or less precision than others. As such, MOEs and the percentile of regulation are not "bright lines." The Agency has focused its sensitivity analyses on MOEs of 10 and the 99.9th percentiles of exposure as points of reference, not as required thresholds, values, or cut-points.

When developing any risk assessment, assumptions must be made in areas where data are not available; this is the also case for the NMC CRA. In the NMC CRA, the Agency has made health protective assumptions in its baseline analysis, particularly regarding which years of PDP data are most appropriate for use in the CRA and the inter-species extrapolation factors for those NMCs without human data. The sensitivity analyses shown and discussed here are designed to evaluate the degree to which key areas of the risk assessment under- or over-estimate the cumulative risk in an effort to characterize and understand the MOEs presented in this assessment. As described in detail above, the Agency has conducted four sensitivity analyses on the food assessment. The results of these sensitivity analyses were discussed earlier in this chapter and are summarized in Table I.G-6.

Table I.[STYLEREF 2 \s]-[SEQ Table * ARABIC \s 2]. Summary of NMC Cumulative Food Assessment: Sensitivity Analyses.

Sensitivity Analysis	Age Group	Estimated Exposure at the 99.9th Percentile (mg/kg oxamyl equivalents)	MOE at the 99.9th Percentile	Percentile at which Target of 10 is Reached
1. Baseline CRA	Children 1-2	0.0229	7.9	99.848th
	Children 3-5	0.0209	8.6	99.870th

2. LOD of PDP: Replace 0s with one-half LOD	Children 1-2	0.0238	7.6	99.833th
	Children 3-5	0.0217	8.3	99.859th
3. Recent PDP Data Only (2002-2006)	Children 1-2	0.0185	9.8	99.895th
	Children 3-5	0.0170	10.6	N/A
4. Summing Exposure over 24 Hours	Children 1-2	80% of individuals at the 99.8th percentile of exposure and above were due to exposures from one eating event		
	Children 3-5			
	Children 1-2	0.0220	8.2	99.86th a
	Children 3-5	0.0196	9.2	99.88th a
5. CSAF Approach for Inter-species UF	Children 1-2	0.0183	9.8	99.896th
	Children 3-5	0.0171	10.5	N/A
Recent PDP Data only & CSAF Approach for Inter-species UF	Children 1-2	0.0160	11.3	N/A
	Children 3-5	0.0147	12.3	N/A

[a] These percentiles are reported to only four significant digits since they are produced by the ORD SHEDS model and only reported to two decimal places

As can be seen, these four sensitivity analyses result in only minimal changes to the estimated cumulative exposure to the NMCs through the food pathway and did not result in meaningful changes in the associated MOEs. These results support the Agency's assumptions and findings that:

- residues below the LOD can be assumed to be "zero" for the cumulative risk assessment without underestimating to any substantial degree the cumulative risk to these pesticides. For children 1-2 and 3-5 years, MOEs reach the target of 10 at the 99.833th and 99.859th percentiles of exposure when the one-half LOD assumption is applied. These percentiles at which MOEs of 10 are reached are not meaningfully different from those under the Agency's baseline assumption.

- using only the most recent PDP data (as opposed to all relevant PDP data from 1994-2006[t]) does not result in substantive changes in exposure estimates or associated MOEs. For children 1-2 and 3-5 years, MOEs reach the target of 10 at the 99.895th and >99.9th percentiles of exposure respectively, when only the most recent PDP data is used. These percentiles at which MOEs of 10 are reached are not meaningfully different from those under the Agency's baseline assumption.

- the cumulative estimates of food exposure provided by summing exposure over 24 hours do not substantively overestimate cumulative exposure to food. Food exposure to NMCs most often occurs at one eating event such that incorporating recovery between eating events is not necessary.

- using the CSAF approach for the inter-species UF does not result in substantive changes in exposure estimates or associated MOEs. For children 1-2 and 3-5 years, MOEs reach the target of 10 at the 99.896th and >99.9th percentiles of exposure, respectively, when using the CSAF approach to adjust the inter-species UF from 10x to 3x for carbaryl, carbofuran, and formetanate. These percentiles at which a MOE of 10 is reached are not meaningfully different from those under the Agency's baseline assumption.

In addition, Table I.G-6 shows the combined impact of using only the recent PDP data and the CSAF approach for the inter-species factors on the cumulative food estimates. When evaluating these two aspects simultaneously, MOEs for all age groups, including children 1-2 and 3-5 years increase to 11 or greater.

The food risk assessment is considered highly refined and is designed to provide realistic estimates of exposure to NMCs. Some assumptions used in single chemical risk assessments have been removed in the CRA to prevent compounding conservative assumptions when assessing the combined risk to the 10 NMC pesticides comprising the cumulative assessment group. Even with the highly refined nature of this cumulative risk assessment, there are still conservative assumptions used in the baseline estimates of cumulative risk. The Agency has evaluated the effect of a

[t] The Agency has used all years of PDP except in cases where use patterns have been changed in the baseline analysis. Specifically, use patterns have changed for carbaryl, methomyl, formetante HCl, and carbofuran.

number of these assumptions in its sensitivity analyses conducted for the food assessment and found that they result in only minimal changes to the estimated cumulative exposure to the NMCs through the food pathway and did not result in meaningful changes in the associated MOEs. Further, the Agency has a high level of confidence that the cumulative risks are not under- or over-estimated based on these results.

4. Residential Assessment

The residential component of the revised NMC cumulative risk assessment is a probabilistic assessment, which applies distributional analysis to residential exposure assessments. In addition to incorporating distributional analysis, the assessment also factors in the seasonal and regional aspects of pesticide use. Three types of data are used in the residential assessment:

- Pesticide use,
- Pesticide residue dissipation, and
- Exposure contact/human exposure factors.

Pesticide use data are used to determine the percent of households using a pesticide, the timing of the pesticide treatments, and frequency and duration of exposure. In the revised NMC CRA, all pesticide use data were based on pest pressures in the Southeast region of the U.S. While insect growth may slow during the winter months in the South, unlike other regions in the country, there is no period of dormancy. Residential exposure to pesticides is greatest in this region due to the longer periods of pest pressure. Consequently, this assessment as a whole is assumed to provide a worst case estimate of exposure.

Pesticide residue dissipation data address the fate of the pesticides once applied to an environment (e.g., lawns). Exposure contact data are exposure-specific metrics that relate human exposure to pesticide residues. Humans come in contact with the residues by contacting the product directly or by contacting the residues left after the pesticide applications are made. Distributions of human exposure factors, such as the body weight assumption used in this assessment, come from the Agency's Exposure Factors Handbook (USEPA, 1997a). The exposure factors taken from the Agency's Exposure Factors Handbook have been previously characterized and are used throughout the Agency.

a. **Pesticide Use Data**

Accurate pesticide use data, including information on regional site/pest markets, timing of application and the percent of households using NMC products, are key to the residential risk assessment. In the absence of that specific pesticide use information, OPP developed residential exposure scenarios based on timing aspects found in survey data from the Residential Exposure Joint Venture (REJV), regional Cooperative Extension Service publications, and Doane's GolfTrak. While the REJV data contains a complete 12-month pesticide use diary for 1,217 household-users, use of these NMCs by homeowners is a relatively infrequent event, leading to relatively high uncertainty around the various pesticide use estimates. Additionally, the REJV did not collect information on the purpose of use (pest treated), areas treated, or application rates. Therefore, REJV data was used in combination with professional judgement, and product label and pest pressure information from the Cooperative State Extension Services to estimate application frequency and timing. Doane's GolfTrak was used to identify the percent of golf courses treated with pesticides. OPP believes this is a robust data source.

b. **Pesticide Residue and Exposure Contact Data**

i. Dermal Exposure

Applicator Exposure

Dermal exposure to pesticides may occur during application and post-application activities. Examples of application activities that might result in pesticide exposure include, but are not limited to, spraying liquid pesticide formulations on ornamental plants, or applying granular formulations to residential turfgrass.

The application of pesticides is one of the more straight-forward activity patterns to measure because it represents easily defined activities. As a result, dermal exposure contact data used to assess exposures during application of consumer-oriented pesticides are the most robust information used in the residential portion of this assessment. Recent data generated by ORETF have been used to assess the use of hose-end sprayers (lawn care products), rotary granular spreaders (lawn care products), and hand-pump sprayers (home gardens and orchards) and hand-held dusters (home vegetable gardens). Another study, submitted by a registrant, was also used to assess residential applicator exposure using granular shaker cans. All

studies meet or exceed current Agency guideline requirements (in particular regarding the number of monitoring units) and can be extrapolated to include clothing scenarios ranging from short-sleeved shirts and short pants to long-sleeved shirts and long pants. OPP has high confidence in these data.

Post-Application Exposure

Examples of post-application activities that might result in pesticide exposure include, but are not limited to, weeding and harvesting home gardens, mowing and playing on lawns, and playing golf. There are several post-application dermal exposure scenarios addressed in this assessment. These are: post-application dermal exposure resulting from lawn care products, garden and home orchard products, pet collar products, and contact with treated golf courses.

Like the applicator scenarios, the post-application garden and home orchard exposure scenarios are easily defined. For harvesting vegetables or weeding, there is a substantial amount of data on farm worker exposures. These contact values have the potential to overestimate residential exposure, since they are based on activity patterns of individuals whose pay is based largely on their productivity. Professional harvesters are likely to be more efficient than most home gardeners, and therefore exposed to a greater amount of treated surface. Because home gardens consist of a wide variety of plants, the use of a uniform distribution of values represents activities as diverse as hoeing and harvesting. These values may overestimate early season activities that consist predominantly of potential exposure to small plants.

There are a variety of dislodgeable foliar residue data available for carbaryl. Dislodgeable residue data for sunflowers were used to assess the vegetable and ornamental garden scenarios, while olive tree dislodgeable data were used to assess the fruit tree scenario. These dislodgeable data were scaled in accordance with the label application rates for the carbaryl home garden and orchard products. Chemical-specific residue data for crops with foliage similar to those typically found in home gardens and orchards are expected to adequately represent residues found on home-grown ornamentals, fruit, and vegetables.

Dermal exposure from post-application contact with lawn chemicals is varied. Contact data, representative of the range of human activities on lawns has been difficult to model.[u] Dermal contact

[u] The August 2005 SAP recommended performing a sensitivity analysis to compare exposure estimates that result when distributions are entered both with and (then) without truncation of distributions that extend (at least theoretically) to infinity. More specifically, the preliminary NMC CRA

exposure values were identified for adults who performed scripted activities (Vaccaro, 1996). Rates of transfer in the studies with surrogate compounds were similar to those observed in the chemical specific dissipation data available to OPP.

Granular turf transferable residue (TTR) data are available for carbaryl, the only chemical registered for residential lawn use considered in this assessment. These residue data were used to calculate post-application dermal exposure for the broadcast use of carbaryl on residential lawns. Because the current mitigation for carbaryl lawn products limits broadcast applications to granular formulations only, these data are expected to adequately estimate dermal exposures resulting from broadcast applications to the lawn.

The current assessment also addresses dermal post-application exposure for adults and teens playing rounds of golf on treated courses. Carbaryl liquid TTR data were used to assess risk for this scenario. Because golf course turf is intensively maintained (generally watered and mowed every day), these residue data are assumed to overestimate residues on treated golf course turf. The exposure contact factors used to estimate post-application dermal exposure are based on a few measurements from two studies that assessed golfer exposure. The exposure duration for individuals playing golf was assumed to be two to four hours per day based on information obtained from a 1992 survey conducted by the Center for Golf Course Management. These assumptions are expected to adequately estimate potential exposure for golfers.

The revised NMC CRA also considered exposures through the use of flea collar products for carbaryl and propoxur. Estimates of exposure for these scenarios were developed using an approach similar to the one taken with the turf care products. The dermal contact factor(s) for post-application exposure is based on a shampoo and groomer exposure study for carbaryl in which each groomer shampooed the dogs, picked them up wet, and placed them into crates. The dogs were then dried and groomed. These activities are likely to result in higher contact factors than intermittent contact with a pet wearing a collar and thus provide a conservative estimate of exposure.

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that was presented to the SAP in September 2005 truncated any lognormally distributed input parameter at a high end percentile (99th) since values associated with higher percentiles were considered to be unrealistic. As part of this revised NMC CRA, OPP performed a sensitivity analysis to evaluate the impact of truncation on the residential scenario that was found to have the greatest influence on the NMC CRA results. Specifically, OPP utilized the full (untruncated) lognormal distribution for the transfer coefficient parameter to estimate dermal exposure to treated lawns. This full (untrucated) distribution extends to infinity implying no limit to how high the transfer coefficient can be. The results of this sensitivity analysis (not presented here) indicate that truncation at the 99th percentile in our baseline assessment had no significant effect on the results of the NMC CRA.

ii. Non-dietary ingestion

Toddler ingestion via hand-to-mouth activity was the only oral route of exposure considered in the residential portion of this assessment. Specifically, oral hand-to-mouth ingestion was considered only for children 1-2 and 3-5 years old for the lawn care and pet collar scenarios.

In the preliminary NMC CRA, the non-dietary oral exposure pathway produced the lowest Margins of Exposure (MOEs), and would therefore be of greatest concern to the Agency. These low MOEs were mainly due to the incorporation of micro-activity data into our macro activity models which are based on daily average activities (and thus use a daily time step). The non-dietary ingestion pathway was the least refined of the residential exposure pathways modeled in the preliminary NMC CRA. In the revised NMC CRA, OPP has modified the methodology used to assess this pathway. This refined methodology is based on comments and input from the FIFRA Scientific Advisory Panel, and the SHEDS and CARES developers.

The Calendex model used in the preliminary and the revised NMC CRA is a macro activity model. Specifically, this model simulates exposures by randomly drawing values for each of the various exposure factors (e.g., exposure duration, frequency of hand to mouth events, surface area of hand mouthed per event) then multiplying these values together per the OPP Residential Standard Operating Procedures algorithm (USEPA, 1997b). The distributions for many of these exposure factors were obtained from micro-activity data. For example, the distribution for frequency of hand-to-mouth events was based on data from observational studies in which all hand contacts were recorded as hand-to-mouth events, regardless of the fraction of hand mouthed. For the fraction of hand mouthed, no adjustment was made for the duration of time the hand remained in the mouth. Utilizing such micro-activity data with macro activity models poses many challenges. For example, if two variables are negatively correlated (e.g., more frequent mouthing is associated with smaller areas of hand mouthed), then "modeling the product of two jointly distributed variables as independent draws will overestimate the variances…or overestimate exposure at the high end." Similarly, "fixing the residue on a child's hands (and/or other exposure factors) for a two hour play period…will yield 'greater variability in the modeled distribution of exposures than a run that updates the residue concentration hourly during the exposure." (FIFRA SAP, 2005b).

The new algorithm establishes a maximum amount of residue that can be on the hand, or a maximum dermal loading. The amount of non-dietary oral ingestion increases with the exposure duration, the

frequency of hand-to-mouth events per hour, and the surface area mouthed per event, while the hand loading serves as an upper constraint on oral ingestion between replenishment events. This approach is a refinement of the approach used in the preliminary NMC CRA and is better suited for assessing children's hand-to-mouth exposure in a probabilistic model.

The MOEs for all residential scenarios assessed in the NMC CRA were derived from a combination of data from multiple sources. The data sources used in the NMC residential assessment rely upon the best available data. However, each data set introduces possible uncertainties in the outcome of the exposure assessment. Post-application exposures from the lawn and pet uses are considered to be the most significant source of uncertainty in the residential risk assessment. A summary of these uncertainties and their direction and magnitude, is presented in Table I.H.1. The assumptions made in this assessment provide a reasonable, high-end estimate of cumulative exposure to NMC residential products. OPP is confident that the residential assessment is sufficiently conservative and will not underestimate exposure or risk.

Table I.[STYLEREF 2 \s]-[SEQ Table * ARABIC \s 2]. Input Parameters Used in the Exposure Models: Bias, Assumptions, Uncertainties, and Strengths

Model	Input Parameter	Exposure Bias	Assumptions, Uncertainties, or Strengths and Other Comments

Exposure Model for Residential Pathway	Human Activity Pattern	+ = upward ~ = neutral - = downward	

Lawn Exposure	Unit Exposure: push-type rotary spreader (mg exposure per amount of active ingredient applied)	+	Assumptions/Uncertainties This unit exposure value is based on 30 replicates consisting of individuals using a push-type rotary spreader. A number of clothing scenarios are possible to be generated from these data. In this assessment short-sleeved shirt and short pants were assumed. This may overestimate exposure as large portion of exposure is to the lower legs. Although a surrogate compound was used, exposure is believed to be more influenced by the type of equipment used rather being chemical specific. OPP has high confidence in these data. A lognormal distribution was used for the Unit Exposure (UE). Assumed gloves are not worn. Survey data do indicate that some residential handlers use gloves and thus this may overestimate exposure for these residential handlers. However, because consumers are unlikely to use, remove and care for PPE in the manner of professionals, it is unclear what impact this may have on actual use. The surrogate compound (dacthal) used in the exposure study may be dustier than the granular formulations of the NMC compounds assessed. This factor increases confidence that this variable will not underestimate exposure.

	Area treated (square feet)	- to ~	Assumptions/Uncertainties A difficult variable to estimate. However, the assumption is reasonable given the application equipment used. Although may underestimate areas that have larger lawns (Midwest), margins of exposure are large.

	Dermal Contact Transfer	~ to +	Adults: activities performed with tank tops and short pants, lognormal distributions may be reflective of study design rather than actual activities (choreographed) Children: Based above scripted activities study and adjusts transfer factors for differenced in body weight and surface area between adults and children. Assumes all adults and children living in households being treated with lawn care products are exposed (enter treated area).

	Turf Residues: dermal and hand-to-mouth	~	Chemical specific data for granular formulation of carbaryl.

	Frequency of hand-to-mouth events and surface area of hand mouthed	~	Based on analysis of the best available observational data (Xue et al, 2007).

	Duration on lawn	+	For children, the value used actually measured time spent outdoors and not just time spent on lawns. Does not account for survey responses of individuals that did not play on lawns or go outside.

Home Garden, Fruit Trees, and Ornamental Plants	Applicator: Hose-End Sprayer, Dust Shaker Can, Trigger Pump Sprayer, Handwand	~ to +	All UE data for these scenarios are chemical-specific. In this assessment short-sleeved shirt and short pants were assumed. This may overestimate exposure as large portion of exposure is to the lower legs and upper arms. Although a surrogate compound was used, exposure is believed to be more influenced by the type of equipment used rather being chemical specific. OPP has high confidence in these data. A lognormal distribution was used. Assumed gloves are not worn. Survey data do indicate that some residential hand

	Area treated: ornamentals	~ to +	Assumes all plants are treated around the perimeter of an average-sized house.

	Area treated: vegetables	~	A lognormal distribution of a well studied variable.

	Area treated: fruit trees	+	Assumes all fruit trees are treated with the maximum labeled application rate. Little data to determine actual area occupied by home orchard.

	Postapplication: vegetables/fruits	~ to +	Contact values represent a wide range of activities. All plants are assumed to be treated.

	Postapplication: fruit trees	~ to +	Based on olive dfr study data.

	Plant residues	~	Based on chemical specific DFR data.

Ornamental Snail/Slug Bait	Applicator: Granular	~ to +	This unit exposure is based on 15 replicates. Used study assessing exposure while treating shrubs which had higher unit exposures than for flowers. A lognormal distribution was used.

Pet Collars	Postapplication	~ to +	Dermal contact value from studies in which there was substantial contact. Assumptions for pet fur residues are based on the OPP's SOPs for Residential Exposure Assessment. Based on analysis the best available observational data (Xue et al, 2007).

	Duration	~	Based on data from the Freeman et al, 2001 (few replicates).

Golf	Post-application: Dermal Contact Transfer	~	The surrogate data used to derive transfer coefficients were based on two measurements of four individuals playing golf on two golf courses treated with chlorothalonil (Ballee, 1990), and the exposure of golfers (four volunteers) to flurprimidol (Moran et al., 1987).

	Duration	~	Estimate based on 1992 Golf Course Management Report, describing amount of time spent golfing.

	Turf Residues: dermal	~	Chemical specific data for liquid formulation of carbaryl.

5. Drinking Water Assessment

The regional drinking water exposure assessments are intended to represent exposures from vulnerable drinking water sources resulting from typical NMC pesticide usage. Each regional assessment focuses on areas where combined NMC exposure is likely to be among the highest within the region as a result of total NMC usage, adjusted for relative potencies, and vulnerability of the drinking water sources. The estimated drinking water concentrations for each scenario are not national numbers but are reasonable for people living in those vulnerable areas. For ground water, shallow private wells in highly permeable soil and vadose zone materials with acidic (pH < 7) soil and ground water are expected to be most vulnerable. For surface water, drinking water reservoirs in small, predominantly agricultural watersheds are likely to be most vulnerable.

Because the selection process took into account the relative potencies of the NMC pesticides, the sites used for the initial drinking water exposure estimates are biased toward the areas in which the more toxic NMC pesticides are used. Since the purpose of the assessment is to identify the impact from multiple NMCs occurring in water in the same area, the area(s) selected for the assessment do not necessarily represent the highest exposure of a single chemical, but rather the highest multiple NMC exposure within the region. Since pesticide use may vary from year to year and cropping and usage patterns may change, some areas in other parts of the region may have greater water exposure in a given year.

a. Ground Water Exposure

Based on monitoring studies, pesticide fate and transport properties, and model projections, the Agency believes that the highest overall cumulative NMC concentrations in drinking water sources will be associated with:

- **Shallow wells:** Concentrations will vary with varying depths to ground water and well depths. Higher concentrations would be expected in more shallow wells while lower concentrations would be likely in deeper wells.

- **High leaching potential soils and vadose zone:** Such soils are well-drained, highly permeable, and have low organic matter content.

- **Acidic soil and ground water:** Which favor the persistence of the NMC chemicals, which degrade more rapidly in neutral to alkaline pH conditions.

These conditions have been identified in some areas of the Delmarva Peninsula, the southeastern coastal plain, and Florida (primarily along the central ridge). Estimated NMC exposures in other NMC use areas underlain by less permeable soils or with neutral to alkaline soil and ground water are expected to be considerably lower. While areas of potential concern are illustrated in Figure I.E.7, it does not take into account localized conditions such as type and depth of well, local variations in soil/vadose zone permeability, or acidity/alkalinity of the ground water. It also can not account for the locations of private wells or the population that may be drawing their drinking water from such vulnerable wells.

The estimated NMC concentrations for these vulnerable wells are comparable to available monitoring data under similar conditions, particularly for aldicarb and carbofuran, which are the dominant NMC pesticides in ground water. High concentrations of these pesticides (including both the parent pesticide and degradation products) have been found in wells across the country where the pesticide use coincided with highly permeable soils, shallow ground water, and acidic conditions (summarized in Chapter I.E and Appendices II.E.2 and II.E.7). These detections led to voluntary label changes that restricted the use of those pesticides in some regions or placed conditions under which the pesticides could be used in some soils (for example, the well setback distances added to the aldicarb labels for certain soil and groundwater conditions).

Actual NMC concentrations in private wells may vary from the estimated concentrations as a result of a number of factors. Important conditions that may affect NMC residue levels in drinking water from private wells including depth to ground water, distance between the well and the field of application (setback distance), amount of NMC pesticide applied over time, and soil/vadose zone properties that affect the downward movement of water and pesticides.

i. Depth to ground water

EPA set the water table at 30 feet to represent a shallow private well, based on a number of sources (Berndt et al, 1998; McPherson et al, 2000; USGS, 1990; FL water management districts; monitoring study by Bayer CropScience reviewed by USEPA, 2007a). In the Bayer CropScience study, which surveyed wells in selected aldicarb use areas, 37% of the 800 wells sampled in the southeast (exclusive of Florida) had

reported groundwater depths <50 feet below the surface, with a total of 21% of the wells with reported depths <25 feet below the surface (however, the depth to groundwater was unknown for 45% of the sampled wells). Other factors, such as type of well construction, presence of casing, and depth to well screen will also influence the concentration of NMC residues found in the water. With deeper wells, travel time between the soil surface and ground water will increase, allowing more time for degradation in transit and lower concentrations.

EPA evaluated the potential impact of varying well depth on estimated NMC concentrations in groundwater in Appendix II.E.7. In the central ridge of Florida, estimated concentrations of total aldicarb residues and oxamyl ranged from an order of magnitude greater for wells at 15 feet to a factor of 2-to-4 times lower for wells at 50 feet. A similar range in concentrations was found for total aldicarb concentrations in the southern coastal plain (GA) scenario.

ii. Setback distances between the well and the treated field

For aldicarb, EPA simulated a setback distance between the well and treated field, based on the label specifications: 1000 feet for citrus in Florida; 300-500 feet for other uses in the other regional scenarios. The Agency evaluated the impacts of the assumed label setbacks in Appendix II.E.7. The conceptual model accounted for setback distances by increasing the travel time between the treated field and the well. The effect of the setback is based on the assumption of first-order degradation of aldicarb by hydrolysis during the extra travel time from the field of application to the well.

For aldicarb, a 300-foot setback distance reduced estimated concentrations by a factor of 2 while a 1000-foot setback distance reduced estimated concentrations by a factor of 20. Actual reductions will vary, depending on the direction and velocity of lateral groundwater flow in the field. The Agency does not have any monitoring data in similarly vulnerable areas with which to judge estimated concentrations. While the Bayer CropScience monitoring study showed some differences in frequencies of detection based on soil leaching potential, the study only identified distance between the well and the field, not the area of application.

The well setbacks only apply for certain high-leaching soils where groundwater is within 25 feet of the surface and the well is not cased. For other soils, no setback is specified.

iii. Hydraulic conductivity of the soil/vadose zone

The soils in the central ridge of Florida have very high saturated hydraulic conductivities. Less permeable soils and soils without substantial macropore flow are likely to result in lower than predicted concentrations because of the longer transport time.

iv. Soil/vadose zone and ground water pH

All of the NMC pesticides, except for the parent aldicarb, are susceptible to pH-dependent hydrolysis. Under acidic conditions (low pH), these chemicals persist; under alkaline conditions (high pH), they degrade rapidly. The estimated concentrations reflect acidic conditions. Where soils and water are neutral to alkaline, the concentrations are expected to be lower than those estimated for the preliminary assessment. In general, the soils and ground water in the ground water scenario locations in the NMC CRA – the Central Ridge of Florida, the southeastern Coastal Plain, and the Delmarva Peninsula – are expected to be acidic.

v. Other factors

Label changes for aldicarb, a major contributor to the NMC residue levels in ground water, made in the mid- to late-1990's were intended to reduce the amount of total aldicarb residues reaching ground water in vulnerable areas. These included well setbacks and some water management changes. While the Agency addressed well setbacks in the conceptual model, it did not explicitly account for recommended water management changes on the label. As noted in Chapter I.E, while the private well monitoring data from FL DEP, which analyzed water from the tap rather than from the well, indicate a reduction in total aldicarb residues detected in later years, interpretation of these results has been confounded because the state of Florida has also been placing carbon filters on the taps of those homes with aldicarb detections in well water.

The ground water exposure represents private drinking water wells. The Agency assumed in this assessment that, in general, public water supplies supplied by ground water will typically draw from deeper aquifers and/or aquifers that have a relatively impermeable layer between the surface and the water supply. Such supplies are expected to be much less vulnerable to pesticide contamination. Public water supplies have a higher probability of being treated, although conventional treatments processes are likely to result in little or no reduction of NMC residues in water. However, where lime softening, which will accelerate pH-dependent hydrolysis for all but parent aldicarb, or activated carbon

filtration is used, some reduction in NMC residues between untreated and treated water may occur (Appendix II.E.3).

b. **Surface Water Exposure**

The Agency does not expect cumulative NMC residues in surface water sources of drinking water to reach levels that will contribute substantially to the cumulative exposure. Estimated NMC levels in drinking water surface water sources from the coastal plain of North Carolina were greater than predicted for any of the other regional surface water exposure sites. When the drinking water component was combined with the food and residential exposure routes in the cumulative assessment, the highest seasonal exposures from surface water sources of drinking water were approximately an order of magnitude less than those estimated for food or for the total NMC exposure from all routes. For most of the year, predicted exposures from drinking water were much lower.

For the surface water sources of drinking water, OPP used PRZM/EXAMS to predict pesticide concentrations in a small reservoir. This modeling approach makes certain assumptions regarding the nature of the drinking water source, the watershed, and year-to-year variability.

The reservoir used for the exposure assessment is based on the specific geometry (watershed and reservoir size) of an actual reservoir (Shipman City) in the Midwestern US. As such, it is more representative of potential transport to similar drinking water sources in high rainfall areas such as the Midwest and Eastern U.S. than in the west.

PRZM is not a basin-scale model, but a field-scale model which estimates edge-of-field pesticide loads in runoff. It does not explicitly account for the relative contributions of each field to the reservoir. OPP used a cumulative adjustment factor (a combination of the regional percentage of the total watershed area in crops with carbamate uses and the percentage of acres treated by each carbamate on each crop) to adjust the resulting reservoir concentrations calculated by EXAMS (see USEPA, 2000b, for assumptions involved in applying percent crop area factors for drinking water assessments).

PRZM does not account for location in the watershed: all fields are assumed to be uniformly distributed within the watershed, with runoff going directly into the reservoir. Each crop use simulated in PRZM assumes that the entire area of the watershed planted in the crop consists of a single soil. In each of the regions, OPP used data from local soils on which the crops are grown. When possible, the soil selected for each scenario was a benchmark soil that was prone to runoff

(classified as hydrologic group "C" or "D" soils). While an assessment using a single soil assumes that each part of the watershed will be equally vulnerable to runoff, areas of higher and lower runoff vulnerability will exist in an actual watershed.

Because the application rates, frequencies, and timing are held constant, the PRZM/ EXAMS simulations over multiple years evaluate the impact of the variability in precipitation on the amount of pesticide that reaches surface water. Because weather data spanning 30 years is available for many locations across the country, PRZM/ EXAMS can account for pesticide runoff from a wide range of weather patterns not otherwise possible with monitoring studies that span relatively few years. The age of the weather data (1961 to 1990) limits OPP's ability to compare of the modeling output to more recent monitoring data.

Weather data files for PRZM are available for weather stations across the country. The weather station nearest to the county or counties used for the simulations was chosen for the cumulative assessment. To the extent that precipitation in these counties over the period of record might have been greater or less than that recorded at the nearest weather station, runoff for that area may have been over- or underestimated by PRZM.

c. **Usage Information**

Typical application rates and frequencies for each NMC pesticide on each crop were generated by taking the average (spanning multiple years) of agricultural chemical usage surveys. This assumes that all applications were made at this typical or average rate and that frequencies of applications were constant year to year. Using these typical application rates and frequencies may underestimate water concentrations in years when pest pressure is higher than in our reported years and may overestimate in years when lower amounts of pesticide are used. The usage data were generally not sufficient to conduct a probabilistic assessment over a distribution of actual application rates.

The Agency used typical application rates and acres treated for the NMC assessment because of a low likelihood that all of the NMC pesticides will be used at maximum rates on all of the crop acreage at the same time. In the case of citrus, which resulted in the highest estimated NMC residues in drinking water for this assessment (for private wells along the central ridge), the maximum label rate for aldicarb, the major contributor to total NMC residues, is 4.95 lb ai/A, while the typical rate used was 3.9 lb ai/A. Given that estimated ground water residues are expected to be proportional to the application rate, the total NMC residues for private wells in the central ridge of FL would

be no more than 20 percent greater than that used in the exposure assessment. In the earlier OP cumulative risk assessment, the Agency compared cumulative OP concentrations in surface water estimated using the average application rates with those estimated using maximum label rates. Estimated peak exposures assuming maximum application rates for all pesticides ranged from no difference for the Florida region to 2 to 4 times greater in the Southeast and Mid-south Regions (USEPA, 2002b).

The typical application rates and percent acres treated are derived from state-level data and assume uniform use practices across the state. In actuality, an uneven distribution of application rates and percent acres treated is expected in response to differing pest pressures. Thus, this assumption will underestimate areas where pest pressures may dictate a higher percentage of acres treated in a given year; similarly, it will overestimate areas where low pest pressures will require fewer acre treatments.

d. **Timing of Exposure**

OPP used crop profiles and other relative crop production publications to establish a window for the application date of the pesticide on a particular crop. This window doesn't necessarily reflect the range over which a pesticide will be applied in a particular year, but captures the year-to-year variation in the application dates over time. Thus, in any given year, the timing of application may be clustered within a shorter time-frame than suggested by the application window. However, because of weather and other environmental factors, the timing of intensive pest pressure and/or pesticide application may vary across the window. Thus, while the time series estimated in the drinking water exposures show a definite time period of peak exposures for surface water sources, the actual time of that peak may vary by several weeks, depending on the size of the window of application. Because of the interaction of processes in subsurface transport, there is a damping effect in the concentrations observed in shallow groundwater. A slight seasonal pattern in ground water residue levels is evident in the ground water estimates, but the seasonal patterns in concentrations in ground water are less affected by timing of application.

The date of application can have an effect on the predicted concentrations generated by PRZM/EXAMS for surface water exposure, depending on how near in time the pesticide application coincides with rainfall events in any given year. OPP evaluated the impact of varying the dates of application across the application window on the OP cumulative distribution (USEPA, 2002b). The impact of varying dates of application was most evident at the extremes in the distributions. The ratio in maximum concentrations between the lowest and highest

estimates was a factor of 5 to 6. For 99th and lower percentiles, the differences were not as dramatic, with the ratio between lowest and highest values generally two or less. This analysis only looked at the cumulative OP distribution and did not evaluate variations in individual chemical distributions. This analysis has not been conducted for the NMC cumulative.

In the absence of data to show otherwise, OPP assumed that all of the pesticide applied on a particular crop is done on the same date. While this may be an unreasonable assumption for a large watershed, it is not unrealistic for the size of the watershed or fields overlying shallow aquifers supplying private wells used in this assessment. This assumption may result in higher peaks for surface water, but similar overall average concentrations than if applications are spread out over time. The resulting estimate of exposure may result in a small overestimation bias in the results that will be greater in large than in small watersheds. Little change is expected for ground water.

6. FQPA 10X Factor for the Protection of Infants and Children

The FQPA (1996) instructs EPA, in making its "reasonable certainty of no harm" finding, that in "the case of threshold effects, **an additional tenfold margin of safety** for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account **potential pre- and post-natal toxicity and completeness of data with respect to *exposure* and *toxicity* to infants and children**." Section 408 (b)(2)(C) further states that "the Administrator may use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children." The following discussion synthesizes information discussed in previous sections of this characterization and information from the hazard, food, water, and residential chapters of the NMC CRA to inform FQPA 10X factor for infants and children. Overall, the Agency believes that there are quality data and scientifically supportable methods to account for specific exposure and behavioral patterns of children. Because characteristics of children are directly accounted for in the exposure assessment and the Agency's methods are not expected to underestimate exposure to NMCs, evaluating the potential for increased toxicity to juveniles is the key component in determining the magnitude of the FQPA factors in the CRA.

The previous sections of this risk characterization describe the data sources and models used to generate the food, drinking water, and residential exposure assessments. Overall, there is a high degree of confidence in the exposure data and methodologies used when assessing cumulative risk to children from food, drinking water and

residential exposure. The cumulative exposure assessments are considered to be protective of children and do not understate risk. As such, the Agency has focused its evaluation of the FQPA 10X safety factor on post-natal exposure to juvenile rats.

Comparative cholinesterase studies with post-natal exposures have been shown to provide more sensitive results than DNT studies or from studies using *in utero* only exposures. Thus, comparative cholinesterase studies have been identified for use in the cumulative risk assessment as the most appropriate studies for developing the chemical-specific factor to address the potential susceptibility of infants and children to the effects of NMC exposure. Data from comparative cholinesterase studies have been used to refine the FQPA safety factor for aldicarb, carbaryl, carbofuran, formetanate, methomyl, and oxamyl. For those NMCs (methiocarb, pirimicarb, propoxur, thiodicarb) without such data, the FQPA 10X safety factor is retained. The Agency believes that the refined FQPA factors are protective of infants and children in that high quality data from sensitive populations were used. Moreover, the methods used to perform dose-response have been peer-reviewed multiple times. These methods provide a quality statistical fit to the toxicity data in juvenile and adults.

7. Physiologically-Based Pharmacokinetic Models

PBPK models, which describe the time course disposition of chemicals and their metabolites, could help assess cumulative risk and to evaluate the relationship between variable environmental exposures and dynamic biological processes. Appropriate PBPK models could quantify the cumulative toxicity that can result from multiple exposures (multiple chemicals and multiple pathways) and from exposure to multiple chemicals with a common mechanism or mode of action. While these models are excellent tools, numerous input parameters are necessary for each chemical. Organ-specific thermodynamic parameters (such as tissue to blood equilibrium partition coefficients) are required for each pesticide entering the body and for each of its metabolites. Additionally, values for all of the metabolic rates governing all the biotransformation steps for each pesticide would be necessary as would information on cholinesterase inhibition and potential mixture effects.

Exploratory PBPK models have been developed for some NMCs. Appendix II.B.6 includes a description and results from EPA's work on such a model for carbaryl. Because PBPK modeling techniques offer good promise, continued development and testing of the models is necessary and should be pursued despite the current limitations with respect to the amount of input information required. Pharmacokinetic

studies (*in vivo* and *in vitro* experiments to determine key values for pharmacokinetic parameters and the time course disposition of the compounds in the body) need to be performed with many compounds to determine the key parameters of use in PBPK modeling. It is anticipated that data and methods will continue to improve and evolve as more experience is gained in this area. Although a biological or pharmacokinetic modeling approach would provide another means to determine the cumulative risk for these NMCs, the input parameters for such an approach are not available. Therefore, OPP has applied simple dose addition and used an empirical curve fitting model (i.e., the exponential model) to determine RPFs and PoDs.

8. Conclusions

With the passage of the FQPA (1996), the Agency is required to consider the cumulative risk of pesticides that share a common mechanism of action. The Agency designated the NMCs as a common mechanism group in 2001 and published its preliminary CRA in 2005. Since that time, the Agency has incorporated new hazard and exposure data, assigned uncertainty and safety factors, evaluated comments from the public, addressed comments by the SAP, and made appropriate adjustments due to risk mitigation actions. The NMC CRA is a highly complex, highly refined risk assessment that uses data from multiple sources and multiple models. Because of this complexity, no single value in the assessment should be used to independently arrive at the interpretation of the results. Instead, it is necessary to consider the results as a whole in order to appropriately interpret the results and arrive at conclusions.

This NMC CRA assessment reflects the completed risk mitigation measures that have been proposed or completed as a result of the single chemical assessments as of September, 2007. Since the publication of the preliminary CRA in 2005, many uses of NMCs have been voluntarily cancelled, have had voluntary cancellation requests submitted or have been determined to be ineligible for re-registration. Specifically, the registrations of methomyl on strawberries is undergoing voluntary cancellation, and the registrant has requested that methomyl use on grapes be cancelled. In addition, carbofuran was determined to be ineligible for reregistration and EPA has initiated the process to cancel all domestic uses and to revoke most tolerances; this cancellation impacts risk to the food and drinking water pathway. Residential indoor spray uses of propoxur that may result in non-occupational exposure for children have been voluntarily cancelled. The registrant of aldicarb has agreed to an increase in the well setback distance from 300 feet to 500 feet for aldicarb use on peanuts in the southern portion of the Coastal Plain. Each of these risk mitigation measures provides substantive

reductions in the exposure to NMCs and improvements to the cumulative risk estimates.

Consistent with the mode of action of NMCs, the revised NMC CRA focuses on acute, single day exposures. It presents the estimates of cumulative risks associated with exposures to NMCs in food, drinking water and from residential uses. Contributions from various pathways and routes of exposure are arrayed separately in a set of temporal or time-series plots of MOEs over a period of 365 days so that the reader can assess and evaluate -- on a pathway and/or route- specific basis -- the significant contributors to risk. This practice permits expression of the full range of values for each parameter and facilitates interpretation of the complete risk picture. OPP is confident that the results reasonably represent exposures and risks from food, water, and residential use to the U.S. population.

The food component of the NMC cumulative risk assessment is based primarily upon two extensive, reliable data sets: 1) USDA's CSFII 1994-96/98 and 2) USDA's PDP. The CSFII provides a detailed representation of the food consumption patterns of the U.S. public across all age groups, during all times of the year, and across the US. The PDP data provide a consistent and reliable sample of pesticide residues in the major children's foods, including fruits, vegetables, dairy products, meats, and grains. The data from PDP are collected so as to closely reflect residues in foods, as consumed and are statistically representative of the U.S. food supply. The PDP program utilizes multi-residue analytical methods such that co-occurrence of pesticides in individual samples is captured. These two sources of data provide a firm foundation upon which to assemble other data to develop the NMC cumulative risk assessment. Oxamyl serves as the index chemical and the residue values for the other NMC pesticides were converted to oxamyl equivalents using the RPF approach. After adjustment for processing, these index equivalent residues were then compiled as distributions of cumulative residues by summing them on a sample-by-sample basis. These cumulative residue distributions were combined with distributions of daily food consumption values via a probabilistic procedure to produce a distribution of potential exposures for the general U.S. population and sub-populations using the DEEM-FCID software. The primary advantage of using distributions of pesticide concentrations and consumption values to assess cumulative exposure is that distributions of exposure values are obtained that represent a distribution of realistic scenarios of exposure that describe both probabilities and magnitudes of multi-chemical cumulative exposure through the food pathway.

The drinking water assessment focuses on areas where combined NMC exposure is likely to be among the highest within each region as a result of total NMC usage and vulnerability of drinking water sources. This analysis is based on a probabilistic modeling approach that considers the full range of data and not a single high-end estimate. EPA estimated NMC exposures in drinking water to individuals in the CRA for both ground water and surface water sources of drinking water by region. The regional drinking water exposure assessments represent exposures from vulnerable drinking water sources resulting from typical NMC usage and reflect seasonal variations as well as regional variations in cropping and NMC use. For the majority of the U.S., NMC residues in drinking water sources are at levels that are not likely to contribute substantially to the multi-pathway cumulative exposure. Estimated NMC exposures from surface water sources of drinking water resulted in MOEs well in excess of 10. For most ground water sources of drinking water, NMC exposures are expected to be similarly low. Private wells extending through highly permeable soils and drawing from shallow depths in acidic, unconfined aquifers (also known as water table aquifers) represent what the Agency believes to be the most vulnerable drinking water sources for the NMCs based on available monitoring, current use patterns, and known soil and hydrologic conditions. Those instances where NMC concentrations resulted in MOEs of less than 10 are being addressed with mitigation measures in the single chemical assessments – an increase in the well setback distance from 300 feet to 500 feet for aldicarb use on peanuts in the southern portion of the Coastal Plain and notice of intent to cancel all domestic carbofuran uses. With these mitigation measures, NMC exposures from drinking water result in MOEs that are greater than 10.

There are three NMC chemicals with currently registered residential uses considered as part of the revised NMC CRA in the residential/non-occupational exposure pathway assessment. The residential uses considered in this assessment include the carbaryl lawn and golf course uses, the carbaryl vegetable and ornamental garden use, the methiocarb snail bait use, the carbaryl fruit tree use, and the carbaryl and propoxur pet collar uses. Several reliable data sources were used to define how pesticides are used, how quickly the residues dissipate, how people may come into contact with pesticides (e.g., via dermal or inhalation exposure), and the length of time people might be exposed based on certain activities (e.g., playing on a treated lawn). As with the drinking water assessment, the residential exposure assessment considers seasonal applications and timing as well as regional differences. In the case of regional differences, the revised NMC CRA focused on the Southeast Region of the United States for two reasons; 1) the growing season is longer in the South and the associated pest pressures are therefore greater, and 2) drinking water concentrations are highest in this

region of the country. The residential and groundwater assessments are based on the most highly exposed localized areas within the southeastern region of the United States. Specifically, the drinking water exposure for Georgia was combined with residential exposure in Florida. Pest pressure data for Florida are assumed to address pest pressure for other areas of the country where estimated NMC water concentrations are the highest (such as Georgia and North Carolina). Due to longer periods of pesticide use coupled with higher concentrations of NMCs in ground water, this assessment provides a reasonable worst case estimate of exposure. The results of the residential risk assessment indicate that remaining uses of NMCs in a residential setting– as borne out by the analyses here -- are below OPP's level of concern for all subpopulations.

EPA also evaluated total (combined) MOEs for all three pathways (e.g., multi-pathway, which is the sum of food + water + residential) simultaneously. The multi-pathway MOEs at the 99.9th percentile are approximately 8 and 9 for children 1-2 and children 3-5 years of age, respectively, for the single day results from Calendex. At the 99.9th percentile of exposure, the food pathway is the most significant contributor. These multi-pathway results are consistent with – and essentially dominated by -- the food results found in Table I.G-5. Because the exposure through food is the dominant exposure pathway for the revised NMC CRA, the total MOEs derived from the multi-pathway assessment are virtually identical to the MOEs from exposure through the food pathway.

The sensitivity analyses shown and discussed here are designed to evaluate the degree to which key areas of the risk assessment may or may not under- or over-estimate the cumulative risk in an effort to characterize and understand the MOEs estimated in this assessment. When developing any risk assessment, assumptions must be made in areas where data are not available; this is the also case for the NMCs. In the revised NMC CRA, the Agency has made health protective assumptions in its baseline analysis, particularly with regard to the years of PDP data which are used (for which it used all years of PDP data except in cases where use patterns have been proposed or changed) and the use of inter-species extrapolation factors for those NMCs without human data. The sensitivity analyses shown here demonstrate that the Agency has not under-estimated exposures and associated risks since many of the modified scenarios result in only small changes in the percentile at which an MOE of 10 is reached.[22]

[22] More specifically, the complex nature of this CRA has been stressed, and the many, varied data sources used to develop quantitative estimates of exposure have been described. Although there is a high level of confidence in this assessment, it is important to recognize the limits on the precision of the estimates generated by the assessment. For example, although the percentiles

The Agency has developed a highly refined and complex cumulative risk assessment for the NMCs that represents the state of the science regarding existing hazard and exposure data and the models and approaches used. The Agency notes that the risk mitigation efforts of the past several years have significantly reduced risk from NMCs in the food, drinking water and from residential use in the US. Taking into account these reductions and acknowledging that several key assumptions are designed to minimize the potential to underestimate exposure and risk, the Agency concludes that, based on the results of the revised NMC CRA, there is a reasonable certainty that no harm will result from exposure to the NMC pesticides covered by this assessment, taking into account the cumulative effects of such residues. Accordingly, the pesticide tolerances for the NMCs covered by this risk assessment are considered to be "safe" as defined in FFDCA section 408(b)(2)(A), and to be reassessed for purposes of FFDCA section 408(g).

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have been reported out to 5 significant figures (e.g., 99.854), the Agency does not believe that the assessment has the power to discriminate between different tenths or hundredths of percentiles of exposure. Put another way, there is no meaningful difference between the exposure received by the 99.9th and the 99.8th percentile of a subgroup, much less between the 99.85th and 99.86th percentiles. The magnitude of actual exposure experienced by a particular percentage of the population is likely to be close to, but somewhat below, EPA's estimate for that percentile. Actual exposure for, say, the 99.9th percentile may fall within the values estimated for the 99.85th and the 99.95th percentiles. But EPA does not believe that the assessment reliably predicts the precise difference in exposure levels for people falling at different points on the distribution when the points are separated by no more than 0.1% difference. Therefore, for risk management purposes, it is also appropriate to considere the percentile at which the estimated MOE for a subgroup reaches 10. If that percentile is not meaningfully different from the 99.9th percentile, as is the case here, it can be regarded as an additional consideration to support the conclusion that there is reasonable certainty no harm will result from cumulative exposure to NMCs.

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II. Appendices

A. Summary of Risk Mitigation for Individual N-Methyl Carbamates[23]

Decision Document	Use Site	Mitigation	Residential Uses Remaining
ALDICARB			
09/2007 RED	Alfalfa grown for seed	Cancelled	None
	Coffee	Cancelled	
	Ornamentals	Cancelled	
	Pecans	Cancelled	
	Sorghum	Cancelled	
	Sugarcane	Cancelled	
	Tobacco	Cancelled	
	Cotton	Rate Reductions	
	Soybean		
	Dry Beans	Geographic Use Restrictions	
	Soybean		
	Sugar Beet		
	Sweet Potato		
	Peanuts	500 foot well setback and application restrictions	

[23] This summary only captures those mitigation measures likely to impact the cumulative risk assessment. It does not include specific mitigation measures intended to protect workers (e.g., REIs, PPE) or to address ecological risks (e.g., spray drift measures, buffer zones for non-target plants).

Decision Document	Use Site	Mitigation	Residential Uses Remaining
CARBARYL			
06/2003 IRED	Wheat	Cancelled - tolerance retained	Liquid lawn use is limited to spot treatment only (<1000 ft.); packaged in pint-size ready-to-use (RTU) hose-end sprayers For garden/ornamental dust products used on vegetables/ornamentals, all end-use products are to be packaged in RTU shaker can containers with ≤0.05 lb ai/container. Granular products are available for lawncare (drop or rotary spreader); for home-garden use granular products packaged in RTU containers only.
	Broadcast applications of liquid formulations to turf EXCEPT sod farms, golf courses, commercial landscape areas and cemeteries	Cancelled	
	Applications by hand, spoon, and belly grinder	Cancelled	
	Pet uses EXCEPT pet collars	Cancelled	
	Corn	Granular and Bait Formulations Prohibited	
	Grain sorghum		
	Alfalfa		
	Rice		
	Sunflowers		
	Asparagus	Rate Reductions	
	Citrus		
	Field Corn		
	Stone Fruit		

Decision Document	Use Site	Mitigation	Residential Uses Remaining
CARBOFURAN			
08/2006 IRED	Alfalfa	Not eligible for reregistration - Import tolerances retained for banana, coffee, sugarcane and rice	None
	Artichoke		
	Banana		
	Barley		
	Coffee		
	Corn		
	Cotton		
	Curcubits		
	Grapes		
	Oats		
	Pepper		
	Plantain		
	Potato		
	Sorghum		
	Soybean		
	Sugar Beet		
	Sugarcane		
	Sunflower		
	Wheat		
	Spinach for seed	Cancelled with a 4 year phase out	
	Chili Peppers		
	Sunflowers		
	Artichoke		
	Cucurbits- granular formulation		

Decision Document	Use Site	Mitigation	Residential Uses Remaining
FORMETANATE HYDROCHLORIDE			
03/2006 IRED	Plums	Cancelled	None
	Prunes	Cancelled	
	Pome Fruit	Application Restrictions	
	Stone Fruit		
	Citrus		
	Orchard crops- aerial application	Prohibited	
METHIOCARB			
03/1994 RED	All food uses	Cancelled	Ornamental woody shrubs and vines, household/ dwellings outdoor premises
	Granular formula	Package size restrictions	
METHOMYL			
12/1998 RED	Grapes*	Cancelled in 2007	None
	Strawberries**		
	Broccoli	Reduction in Max. Seasonal Rates	
	Cabbage		
	Cauliflower		
	Celery		
	Chinese Cabbage		
	Corn, Sweet		
	Lettuce, Head		
	Tomato		
	Peaches	Reduced Max. Single Application Rate	
	Commercial sod farms		
OXAMYL			
12/2000 IRED	Seed piece dip (yams)	**Cancelled**	None
	Soybean		
	Soil broadcast treatment for cotton		
	All Crops	Rate Reductions	
PIRIMICARB- No Mitigation Necessary			
PROPOXUR			

Decision Document	Use Site	Mitigation	Residential Uses Remaining
09/1997 RED	Indoor Residential Uses for Crack and Crevice Treatments***	Cancelled in 2007	Indoor: pastes, tape/strip/patches, baits, and shelf paper Outdoor uses: Structural perimeter applications, spot treatments to wasp nests and ant hill, insecticidal tape for boat mooring lines
THIODICARB			
12/1998 RED	Cole crops	Reduced Single and Seasonal Application Rates	None

* Voluntary cancellation request received September 14, 2007.
** FR Notice announcing receipt of voluntary cancellation published on April 25, 2007 with a 180 day comment period which closes 10/22/07.
*** Use deletion finalized on September 10, 2007.

B. Hazard

1. Data Spreadsheets of the NMC Pesticides

A CD containing the data in this appendix may be obtained by contacting the Office of Pesticide Programs Public Docket

Docket # EPA-HQ-OPP-2007-0935

One Potomac Yard
12777 S. Crystal Drive
Room S-4400
Arlington, Virginia. 22202

703-305-5805

Monday through Friday, 8:30 am – 4:00 pm

2. **Dose-Response modeling of the NMC pesticides**

A CD containing the data in this appendix may be obtained by contacting the Office of Pesticide Programs Public Docket

Docket # EPA-HQ-OPP-2007-0935

One Potomac Yard
12777 S. Crystal Drive
Room S-4400
Arlington, Virginia. 22202

703-305-5805

Monday through Friday, 8:30 am – 4:00 pm

3. **N-M-Carbamate Dose Response**

A CD containing the data in this appendix may be obtained by contacting the Office of Pesticide Programs Public Docket

Docket # EPA-HQ-OPP-2007-0935

One Potomac Yard
12777 S. Crystal Drive
Room S-4400
Arlington, Virginia. 22202

703-305-5805

Monday through Friday, 8:30 am – 4:00 pm

4. **R-packages with file names**

A CD containing the data in this appendix may be obtained by contacting the Office of Pesticide Programs Public Docket

Docket # EPA-HQ-OPP-2007-0935

One Potomac Yard
12777 S. Crystal Drive
Room S-4400
Arlington, Virginia. 22202

703-305-5805

Monday through Friday, 8:30 am – 4:00 pm

5. Summary AChE protocol evaluations, mixture experiments, motor activity measurements

A CD containing the data in this appendix may be obtained by contacting the Office of Pesticide Programs Public Docket

Docket # EPA-HQ-OPP-2007-0935

One Potomac Yard
12777 S. Crystal Drive
Room S-4400
Arlington, Virginia. 22202

703-305-5805

Monday through Friday, 8:30 am – 4:00 pm

6. Physiologically-Based Pharmacokinetic Modeling for the NMC CRA

A CD containing the data in this appendix may be obtained by contacting the Office of Pesticide Programs Public Docket

Docket # EPA-HQ-OPP-2007-0935

One Potomac Yard
12777 S. Crystal Drive
Room S-4400
Arlington, Virginia. 22202

703-305-5805

Monday through Friday, 8:30 am – 4:00 pm

C. Food

1. The Sources of Residue Inputs for the Assessment of the Cumulative Dietary Exposure to N-Methyl Carbmate Pesticides on Foods

A CD containing the data in this appendix may be obtained by contacting the Office of Pesticide Programs Public Docket

Docket # EPA-HQ-OPP-2007-0935

One Potomac Yard
12777 S. Crystal Drive
Room S-4400
Arlington, Virginia. 22202

703-305-5805

Monday through Friday, 8:30 am – 4:00 pm

2. Summary of PDP Residue Analyses of N-Methyl Carbamate Pesticides on Food Commodities Included in Revised NMC CRA

A CD containing the data in this appendix may be obtained by contacting the Office of Pesticide Programs Public Docket

Docket # EPA-HQ-OPP-2007-0935

One Potomac Yard
12777 S. Crystal Drive
Room S-4400
Arlington, Virginia. 22202

703-305-5805

Monday through Friday, 8:30 am – 4:00 pm

3. Processing Factors Used to Estimate Residues of N-Methyl Carbamate Pesticides in Food Forms*

A CD containing the data in this appendix may be obtained by contacting the Office of Pesticide Programs Public Docket

Docket # EPA-HQ-OPP-2007-0935

One Potomac Yard
12777 S. Crystal Drive
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Arlington, Virginia. 22202

703-305-5805

Monday through Friday, 8:30 am – 4:00 pm

4. Translation of Residue Source Data to FCID Food Forms

A CD containing the data in this appendix may be obtained by contacting the Office of Pesticide Programs Public Docket

Docket # EPA-HQ-OPP-2007-0935

One Potomac Yard
12777 S. Crystal Drive
Room S-4400
Arlington, Virginia. 22202

703-305-5805

Monday through Friday, 8:30 am – 4:00 pm

5. Summary of Residue Distribution Inputs to DEEM-FCID for the Revised NMC CRA

A CD containing the data in this appendix may be obtained by contacting the Office of Pesticide Programs Public Docket

Docket # EPA-HQ-OPP-2007-0935

One Potomac Yard
12777 S. Crystal Drive
Room S-4400
Arlington, Virginia. 22202

703-305-5805

Monday through Friday, 8:30 am – 4:00 pm

6. Analysis of Chemicals and Foods in the Upper Portion of the Revised NMC CRA. Exposure Distribution for Children 1-2 Years Old

A CD containing the data in this appendix may be obtained by contacting the Office of Pesticide Programs Public Docket

Docket # EPA-HQ-OPP-2007-0935

One Potomac Yard
12777 S. Crystal Drive
Room S-4400
Arlington, Virginia. 22202

703-305-5805

Monday through Friday, 8:30 am – 4:00 pm

7. Co-Occurrence of N-Methyl Carbamate Pesticides on PDP Samples, 1994-2006

A CD containing the data in this appendix may be obtained by contacting the Office of Pesticide Programs Public Docket

Docket # EPA-HQ-OPP-2007-0935

One Potomac Yard
12777 S. Crystal Drive
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Arlington, Virginia. 22202

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Monday through Friday, 8:30 am – 4:00 pm

8. Comparison of DEEM-FCID version 2.03 and Lifeline version 4.30 Exposure and Risk Estimates through the Food Pathway Only

A CD containing the data in this appendix may be obtained by contacting the Office of Pesticide Programs Public Docket

Docket # EPA-HQ-OPP-2007-0935

One Potomac Yard
12777 S. Crystal Drive
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Arlington, Virginia. 22202

703-305-5805

Monday through Friday, 8:30 am – 4:00 pm

D. Residential

1. Residential Pesticide Use Inputs from REJV Survey Data

A CD containing the data in this appendix may be obtained by contacting the Office of Pesticide Programs Public Docket

Docket # EPA-HQ-OPP-2007-0935

One Potomac Yard
12777 S. Crystal Drive
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Arlington, Virginia. 22202

703-305-5805

Monday through Friday, 8:30 am – 4:00 pm

2. Residential Exposure Scenarios Appendix

A CD containing the data in this appendix may be obtained by contacting the Office of Pesticide Programs Public Docket

Docket # EPA-HQ-OPP-2007-0935

One Potomac Yard
12777 S. Crystal Drive
Room S-4400
Arlington, Virginia. 22202

703-305-5805

Monday through Friday, 8:30 am – 4:00 pm

E. Drinking Water

1. Summary of Surface Water Monitoring Data for NMC Pesticides

A CD containing the data in this appendix may be obtained by contacting the Office of Pesticide Programs Public Docket

Docket # EPA-HQ-OPP-2007-0935

One Potomac Yard
12777 S. Crystal Drive
Room S-4400
Arlington, Virginia. 22202

703-305-5805

Monday through Friday, 8:30 am – 4:00 pm

E-2 Summary of Ground Water Monitoring Data for NMC Pesticides

A CD containing the data in this appendix may be obtained by contacting the Office of Pesticide Programs Public Docket

Docket # EPA-HQ-OPP-2007-0935

One Potomac Yard
12777 S. Crystal Drive
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Monday through Friday, 8:30 am – 4:00 pm

E-3 Drinking Water Treatment Effects on N-methyl Carbamate Pesticides

A CD containing the data in this appendix may be obtained by contacting the Office of Pesticide Programs Public Docket

Docket # EPA-HQ-OPP-2007-0935

One Potomac Yard
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Monday through Friday, 8:30 am – 4:00 pm

E-4 N-methyl Carbamate Usage Estimates

T

A CD containing the data in this appendix may be obtained by contacting the Office of Pesticide Programs Public Docket

Docket # EPA-HQ-OPP-2007-0935

One Potomac Yard
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Monday through Friday, 8:30 am – 4:00 pm

E-5 Chemical-Specific Fate and Transport Properties Used For the Water Exposure Models

A CD containing the data in this appendix may be obtained by contacting the Office of Pesticide Programs Public Docket

Docket # EPA-HQ-OPP-2007-0935

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E-6 NMC Surface Water Exposure Assessment Methods

A CD containing the data in this appendix may be obtained by contacting the Office of Pesticide Programs Public Docket

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E-7 NMC Ground Water Exposure Assessment Methods

A CD containing the data in this appendix may be obtained by contacting the Office of Pesticide Programs Public Docket

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III.Multi-Pathway Graphs

A CD containing the data in this section may be obtained by contacting the Office of Pesticide Programs Public Docket

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One Potomac Yard
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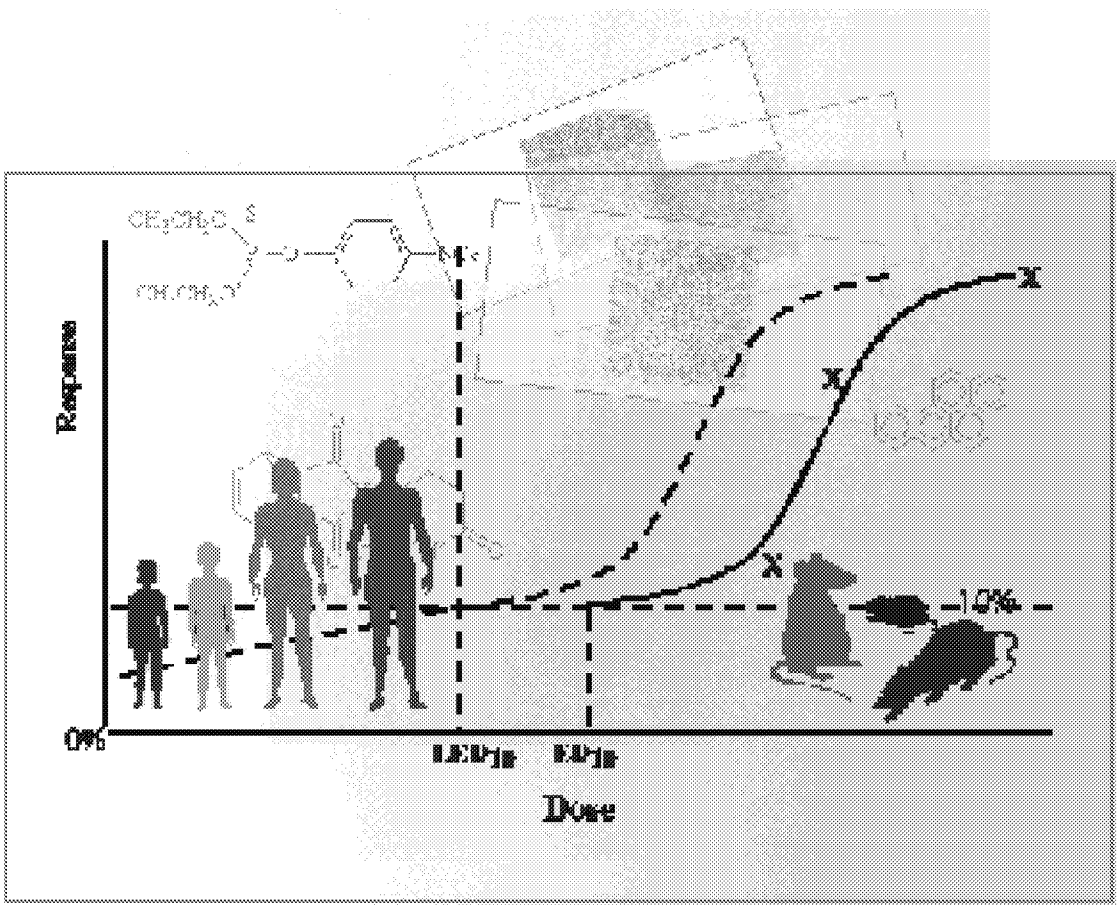
703-305-5805

Monday through Friday, 8:30 am – 4:00 pm

Revised *N*-Methyl Carbamate Cumulative Risk Assessment



U.S. Environmental Protection Agency
Office of Pesticide Programs
September 24, 2007

Revised *N*-Methyl Carbamate Cumulative Risk Assessment
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Technical Executive Summary

With the passage of the FQPA (1996), EPA was required to consider available information concerning the cumulative effects on human health resulting from exposure to multiple chemicals that have a common mechanism of toxicity. In 2001, the Agency identified the *N*-methyl carbamate (NMC) pesticides as a group which shares a common mechanism and published a preliminary Cumulative Risk Assessment (CRA) in 2005. A cumulative risk assessment incorporates exposures from multiple pathways (i.e., food, drinking water, and residential/non-occupational exposure to pesticides in air, or on soil, grass, and indoor surfaces) for those chemicals with a common mechanism of toxicity.

Since the release of the preliminary NMC CRA, the Agency has incorporated new hazard and exposure data, assigned FQPA safety factors, evaluated comments from the public, and addressed comments by the FIFRA Scientific Advisory Panel (SAP). In addition, since 2005, the Agency's Office of Pesticide Programs (OPP) has completed several additional risk assessments for individual NMC pesticides (aldicarb, carbaryl, carbofuran, methomyl and propoxur) and, where necessary, established mitigation measures to be implemented to reduce exposure to these pesticides. These mitigation measures are reflected in this revised NMC CRA.

The methodology used in this revised CRA is similar to that used in the preliminary CRA and supported by the SAP (USEPA, 2005a,b). Throughout the development of this CRA, EPA has relied on the SAP to peer-review guidance documents, methods, approaches, and pilot analyses to ensure that appropriate methods and sound science were applied. In addition to the SAP reviews, EPA has sought and considered public comments on these approaches as it developed these cumulative assessment methods.

Background:

A CRA begins with the identification of a group of chemicals, called a Common Mechanism Group (CMG), which induces a common toxic effect by a common mechanism of toxicity. Pesticides are determined to have a "common mechanism of toxicity" if they act the same way in the body--that is, the same toxic effect occurs in the same organ or tissue by essentially the same sequence of major biochemical events. The NMCs were established as a CMG by EPA in 2001 (USEPA, 2001a) based on the shared structural characteristics and similarities and their shared ability to inhibit acetylcholinesterase (AChE) by carbamylation of the serine hydroxyl group located in the active site of the enzyme. When AChE is inhibited, acetylcholine accumulates and cholinergic toxicity results due to continuous stimulation of cholinergic receptors throughout the central and peripheral nervous systems that innervate virtually every

organ in the body. An important aspect of NMC toxicity is the rapid nature of the onset and recovery of effects; following maximal inhibition of cholinesterase (typically between 15 and 45 minutes), recovery occurs rapidly (minutes to hours).

Once a CMG is identified, it is important to determine which chemicals from that group should be included in the quantification of cumulative risk. The group of pesticides which is included in the quantification of cumulative risk -- and consequently incorporated into the CRA -- is termed the Cumulative Assessment Group (CAG). In determining the specific NMC pesticides to be included in the CAG, EPA considered risk mitigation decisions and exposure potential. EPA identified three exposure pathways of interest for these pesticides: food, drinking water, and residential/non-occupational. Each of these pathways was initially evaluated separately, and -- in performing this portion of the analysis -- EPA determined which of the NMCs were appropriate to include for each given pathway. The cumulative assessment of potential exposure to NMCs in food includes those which are currently registered in the U.S. or have import tolerances. The drinking water exposure pathway includes NMC pesticides with registered uses in the U.S. that can potentially reach water bodies or ground water (i.e., outdoor uses). The revised NMC CRA evaluates the residential exposure pathway for three pesticides registered in the U.S. (carbaryl, methiocarb and propoxur) for home use, The current assessment reflects the most up-to-date and best available information for these chemicals.

There are many steps involved in quantitatively assessing the potential human health risk associated with exposure to the NMC pesticides. The complex series of evaluations involve hazard and dose-response analyses; assessments of food, drinking water, residential/non-occupational exposures; combining exposures to produce a cumulative risk estimate; and risk characterization. These steps are described more fully in OPP's Cumulative Guidance (USEPA, 2002a). The approach to each of these components and their results is briefly explained below:

- Selection of an index chemical to use as the point of reference to standardize the toxic potencies of each NMC, determination of the relative toxic contribution of each NMC, and establishment of a value to estimate potential risk for the group (i.e. point of departure);

- Evaluation of inter-species differences (i.e., extrapolation of rat responses to human responses) intra-species varability; and the potential sensitivity to infants and children;

- Estimation of the risks associated with all pertinent pathways of exposure (i.e., food, drinking water, residential) in a manner that is both realistic and reflective of variability due to differences in location, time, and demographic characteristics of exposed groups;

- Identification of the significant contributors to risk; and

- Characterization of the confidence in the results and the uncertainties associated with the assessment.

Hazard and Dose-Response Assessment:

EPA used the relative potency factor (RPF) method to determine the combined risk associated with exposure to NMCs. Briefly, the RPF approach uses an index chemical as the point of reference for comparing the toxicity of the NMC pesticides. RPFs are calculated as the ratio of the toxic potency of a given chemical to that of the index chemical and are used to convert exposures of all chemicals in the group into exposure equivalents of the index chemical. Because of its high quality dose response data for all routes of exposure, as well as high quality time-to-recovery data, EPA selected oxamyl as the index chemical for standardizing the toxic potencies and calculating relative potency factors for each NMC pesticide.

Toxic potencies for the NMCs were determined using brain AChE inhibition measured at peak inhibition following gavage exposures in rats. Brain AChE inhibition is a direct measure of the mechanism of toxicity and thus does not have the uncertainty associated with using blood measurements of cholinesterase inhibition which serve as surrogates for cholinesterase inhibition in the peripheral nervous system. Furthermore, relative toxic potencies derived from brain data were shown in the preliminary assessment to be similar to those derived from red blood cell data but showed less variability, and thus less uncertainty, when comparing potency across the NMCs.

The Agency used an exponential dose-time-response model to develop benchmark dose estimates at a level estimated to result in 10% brain cholinesterase inhibition (i.e., a benchmark dose or BMD_{10}) to estimate relative potency. The Agency has also calculated the half-life to recovery for brain AChE inhibition. The Agency has used the lower confidence limit on the BMD_{10} (i.e., $BMDL_{10}$) to develop points of departure (PoD) from the oral, dermal, and inhalation routes for oxamyl, the index chemical. A PoD is a point estimate on the index chemical's dose-response curve from which risks associated with the exposure levels anticipated in the human population are extrapolated. EPA compares estimated exposures with the route-specific PoD values to calculate Margins of Exposure (MOE) and to estimate potential risk to humans.

The Agency has used available comparative cholinesterase studies in juvenile (post-natal day 11 and/or 17) and adult rats to evaluate the FQPA 10X safety factor. These studies are available for six NMCs. For these NMCs, the Agency calculated the BMD_{10} in pups and adults—the ratio of these benchmark doses provides the chemical-specific FQPA factor. For the remaining NMCs without comparative data, a 10X factor was applied. For the inter-species extrapolation factors, there are studies with human subjects with three NMCs (aldicarb, methomy and oxamyl) that were determined by EPA, after considering the advice of the Human Studies Review Board, to be ethically and scientifically acceptable for use in this risk assessment. These studies were used to derive the chemical-specific inter-species extrapolation factor for these three chemicals. For the remaining NMCs, the standard 10X factor was assigned for inter-

species extrapolation. Since each NMC has been assigned its own inter-species and FQPA safety factors, the Agency has mathematically applied the value of these factors directly to the RPF for each NMC. In addition, the Agency has used the standard 10X factor for intra-species extrapolation for all the NMCs. Thus, to account for intra-species extrapolation, the target MOE for the revised NMC CRA is 10.

Exposure Assessment:

An important aspect of the exposure analyses is to develop exposure scenarios resulting from the uses for each NMC. Three key pathways of exposure to NMC pesticides -- food, drinking water, and residential and other non-occupational settings -- were included in this assessment. The factors EPA considered in the analysis of exposure by each of these three pathways included duration, frequency, and seasonality of exposure. Evaluation of chemical use profiles allows for the identification of exposure scenarios that may overlap, co-occur, or vary between chemicals, as well as for the identification of populations of concern.

All of the hazard data, exposure data, and exposure scenarios must be combined in a manner designed to produce reasonable and realistic estimates of exposures likely to be encountered by the public in location and time of year. As was done in previous CRAs, EPA used Calendex™ software to integrate various pathways while simultaneously incorporating the time dimensions of the data. Calendex™ provides a focused, detailed profile of potential exposures to individuals across a calendar year. LifeLine™ software was also used to evaluate exposures through the food pathway and these results are presented and discussed in Appendix C. Exposures through residential uses and in drinking water are incorporated into cumulative exposure assessments on a regional basis. EPA conducted regional assessments for drinking water and joined these with generic residential exposure scenarios generally representative of regions in the Southern U.S. These regional assessments reflect the highest potential exposure scenarios for the U.S. and account for differing agronomic uses and reflect the differences in climate, soil conditions, and pest pressures across the country. Exposures that are represented in these generic residential exposure scenarios are not expected to be exceeded in any region in the U.S. Exposure to NMC pesticide residues in foods is considered to be uniform across the nation (i.e., there are no significant differences in food exposure due to time of year or geographic location). The assumption of nationally uniform food exposure is based on the understanding that, to a large extent, food is distributed nationally and food consumption is independent of geographic region and season. The single national estimate of food exposure was combined with region-specific exposures from residential uses and drinking water in three regions that represent the highest potential for exposure.

Table ES -1. Summary Information Regarding the NMC Pesticides and the Uses, and Pathways Included in the revised NMC Cumulative Risk Assessment

Pesticide	Pesticide Uses	Pesticide Pathways		
		Food	Drinking Water	Residential
Carbaryl	Ag Crops	X	X	
	Lawn			X
	Garden			X
	Ornamentals			X
	Fruit Trees			X
	Pet Collar			X
	Golfer Exposure			X
Aldicarb	Ag Crops	X	X	
Oxamyl	Ag Crops	X	X	
Formetanate HCl	Ag Crops	X	X	
Methomyl	Ag Crops	X	X	
Carbofuran	Ag Crops	X	X	
Propoxur	Food Uses	X		
	Pet Collars			X
Methiocarb	Ag Crops	X		
	Ornamental			X
Thiodicarb	Ag Crops	X	X	
Pirimicarb	Ag Crops	X		

The approach for each pathway of exposure and results for the revised NMC CRA are explained below:

Food:

The food component of the revised NMC CRA is considered to be highly refined and to provide reasonable estimates of the distribution of exposures across the U.S. The exposure estimates for food are based on residue monitoring data from the USDA's Pesticide Data Program (PDP) supplemented qualitatively with information from the Food and Drug Administration's (FDA) Pesticide Residue Monitoring Program and Total Diet Study. The PDP data provide a very reliable estimate of pesticide residues in the major children's foods and account -- directly or indirectly through the use of commodity surrogates -- for approximately 93% of food consumption by children. These data also provide direct measures of co-occurrence of NMC pesticides in the same sample. PDP

samples with non-detectable residues were treated in this assessment as "zero" values. Sensitivity analyses have determined that this approach does not significantly underestimate exposures at the upper percentiles for the NMCs (i.e., those percentiles which are of the greatest regulatory importance). For those foods not monitored in PDP, similar commodities that are measured by PDP served as surrogate data sources. This approach is considered to be reasonable and generally sound given that it is based on the concept that families of commodities with similar cultural practices and insect pests are likely to have similar pesticide use patterns and residue levels. Additionally, these surrogated commodities account for less than 1% of children's diets.

The reliability of the food component of this assessment is also supported by the use of the food consumption data from the USDA's Continuing Survey of Food Intakes by Individuals, (CSFII 1994-1996/1998). The CSFII surveyed more than 20,000 individuals over two non-consecutive days and provides a detailed representation of the food consumption patterns of the U.S. public across all age groups, during all times of the year, and across all 50 states. Thus, EPA has confidence that the consumption estimates for food are well-established and consequently support reasonable risk estimates for the U.S. population. The NMC CRA focuses on the following age groups: children 1-2 years old; children 3-5 years old; adults 20-49 years old; and adults 50+ years old. These age groups were selected since they provide a broad representation of potential exposures and because they include age groups that are commonly shown to be the most highly exposed in single-chemical assessments. Details regarding estimated exposures of other age groups are presented in the appendices to this report.

During the period since the issuance of the preliminary NMC CRA in August 2005, the Agency has further improved and refined its assessment of the cumulative risks associated with the NMC pesticides. These refinements include incorporating the most recent food residue data by including pesticide residue data through 2006 from USDA's PDP Program and updating the assessment to reflect individual risk mitigation measures and other use pattern changes for individual NMC pesticides. Specifically, during this period, the Agency has imposed risk reduction measures on some of the major contributors to carbamate cumulative risk. The risk estimates presented in the revised NMC CRA reflect the risk mitigation measures taken on individual carbamates since FQPA was signed into law in August 1996. In general, EPA's risk estimates contained in this CRA reflect mitigation measures that EPA determined to be warranted based on its assessment of the single chemical's risks. Since the preliminary assessment, the Agency has received a request for voluntary cancellation for methomyl on grapes and strawberries, has determined that carbofuran is ineligible for reregistration, and will implement certain label restrictions for aldicarb that will increase drinking water well set-backs in the southeastern coastal plains when certain criteria are triggered. Therefore, these uses (and exposures) are not included and the aldicarb label restrictions have been accounted for in the revised NMC CRA.

In evaluating exposure through the remaining uses on food, OPP concludes that a few uses of NMC pesticides on food crops generally play a larger role in contributing to the cumulative risks of the NMC pesticides. These include use of aldicarb on potato;

carbaryl on peach and strawberry; and methomyl on cantaloupe, watermelon, peach, spinach, and strawberry. However, evaluation of the total risk from exposure to NMCs in foods indicated that the cumulative MOEs from exposure to NMCs do not raise a concern. Specifically, the target MOE of 10 is reached at the 99.848th and 99.870th percentiles of exposure for the most highly exposed age groups, children 1-2 and children 3-5 years old, respectively. These percentiles are not considered meaningfully different from the 99.9th percentile. Associated MOEs range from 7.9 for the most exposed subgroup (children 1-2) to 42 for adults 20-49.

When developing any risk assessment, assumptions must be made in areas where data are not available. In the revised NMC CRA, the Agency has made health protective assumptions in its baseline analysis, particularly with regard to the years of PDP data which are used (for which it used all years of PDP data except in cases where use patterns have changed or will change),the use of a 10x inter-species extrapolation factor for those NMCs without human data, and summing exposures over a 24-hour period. In an effort to characterize and understand the MOEs estimated in this assessment, four sensitivity analyses were performed by the Agency to evaluate the degree to which key areas of the risk assessment may under- or over-estimate cumulative risk. The sensitivity analyses demonstrate that the Agency has not under-estimated exposures through food and associated risks to any significant degree since these sensitivity analyses result in only small changes in the percentile at which the target MOE of 10 is reached. The results of the sensitivity analyses using the most recent PDP data and inter-species factors of 3x instead of the standard 10x for certain pesticides provide added certainty that risks are below the Agency's level of concern.

Residential:

Applications of NMC pesticides in and around homes, schools, offices, and other public areas may result in potential exposure via the oral (due to hand-to-mouth activity by children), dermal, and inhalation routes. There are three NMC pesticides with currently registered residential uses considered as part of the revised NMC CRA in the residential/non-occupational exposure pathway assessment. The residential uses considered in this assessment include the carbaryl uses on lawns, golf courses, fruit trees, and vegetable and ornamental gardens; the methiocarb snail and slug bait use; and the carbaryl and propoxur pet collar uses. In addition to the uses listed above, the preliminary NMC CRA also included an assessment of indoor spray uses of propoxur (crack and crevice). Since the preliminary assessment, the Agency has received a request for voluntary cancellation of all propoxur indoor spray uses that may result in non-occupational exposure for children. Therefore, these uses are not included in the revised NMC CRA.

Another notable change since issuance of the preliminary NMC CRA is the revision of the methodology used to assess children's hand-to-mouth exposure. The non-dietary ingestion pathway was the least refined of the residential exposure pathways modeled in the preliminary NMC CRA. The refined methodology used in this revised assessment is based on recommendations from the August 2005 FIFRA SAP,

and addresses limitations in the non-dietary oral pathway by modifying the probabilistic hand-to-mouth algorithm. This modified algorithm is a product of a collaborative effort between OPP scientists and the developers of the SHEDS (Stochastic Human Exposure and Dose Simulation) and CARES (Cumulative and Aggregate Exposure System) models.

For the residential/non-occupational exposure pathway, several reliable data sources were used to define how pesticides are used, how quickly the residues dissipate, how people may come into contact with pesticides (e.g., via dermal or inhalation exposure), and the length of time people might be exposed based on certain activities (e.g., playing on a treated lawn). As with the drinking water assessment (see below), the residential exposure assessment considers seasonal applications and timing as well as regional differences. In the case of regional differences, the revised NMC CRA considered the Southeast Region of the United States. Due to longer periods of pesticide use, this assessment provides a worst case estimate of exposure.

The results of the residential risk assessment indicate that remaining residential uses of NMCs -- as borne out by the analyses here -- are below OPP's level of concern for all subpopulations.

Drinking Water:

The drinking water assessment focuses on areas where combined NMC exposure is likely to be among the highest within each region as a result of total NMC usage and vulnerability of drinking water sources. This analysis is based on a probabilistic modeling approach that considers the full range of drinking water consumption and concentration data and not single high-end estimates. EPA estimated NMC exposures in drinking water to individuals in the CRA for both ground water and surface water sources of drinking water in each of three regions. The regional drinking water exposure assessments represent exposures from vulnerable drinking water sources resulting from typical NMC usage and reflect seasonal variations as well as regional variations in cropping and NMC pesticide use. Each regional assessment focuses on areas where combined NMC exposure is likely to be among the highest within the region as a result of total NMC usage, adjusted for relative potencies, and vulnerability of the drinking water sources. For ground water, private wells extending through highly permeable soil and vadose zone materials into shallow, acidic ground water are expected to be most vulnerable. For surface water, drinking water reservoirs in small, predominantly agricultural watersheds are likely to be most vulnerable. The co-occurrence of NMC residues in water is estimated primarily from modeling since sufficient monitoring data are not available to be the sole basis for the assessment. However, monitoring data are used to corroborate the modeling results and have helped confirm locations of potentially vulnerable drinking water sources.

In most of the country, NMC residues in drinking water sources are at levels that are not likely to contribute substantially to the multi-pathway cumulative exposure. Estimated NMC exposures from surface water sources of drinking water resulted in

MOEs well above 10. For most ground water sources of drinking water, NMC exposures were similarly low. Shallow private wells extending through highly permeable soils into shallow, acidic ground water represent what the Agency believes to be the most vulnerable drinking water sources for the NMCs based on available monitoring, current use patterns, and known soil and hydrologic conditions. Those instances where NMC concentrations resulted in MOEs of less than 10 are being addressed with mitigation measures in the single-chemical assessments – an increase in the well setback distance from 300 feet to 500 feet for aldicarb use on peanuts in the southern portion of the Coastal Plain and a notice of intent to cancel all domestic carbofuran uses. With these mitigation measures, NMC exposures from drinking water result in MOEs greater than 10.

Combined Pathway (Cumulative) Assessment:

EPA also evaluated total MOEs for all three pathways (food + water + residential) simultaneously. Evaluating exposures is significantly more complex when the analyses address the simultaneous exposures to more than one pesticide and when distributional inputs derived from data from surveys and monitoring studies – as opposed to default assumptions or point estimates – are used. The detailed multi-pathway graphical outputs presented in Part III of this report reflect individual and combined pathway MOEs at multiple percentiles of exposure over the course of an entire year and allow in-depth analysis of interactions of data sets to evaluate potential risk concerns and identify the sources of exposures. The graphical outputs improve the ability to interpret the complete risk picture. Based on the simultaneous evaluation of all three exposure pathways and their associated routes using the Calendex software, the MOEs at the 99.9^{th} percentile are approximately 8 or greater for all populations. Generally, exposures through the food pathway dominate total MOEs, with residential exposures less throughout most of the year. Although still substantially less than exposures through food, dermal exposures from lawn uses of carbaryl dominate the residential pathway. Exposures through drinking water exposures are smaller than exposures through both the food and residential pathways with MOEs exceeding 15 for all scenarios.

Conclusion:

The Agency has developed a highly refined and complex cumulative risk assessment for the NMCs that represents the state of the science regarding existing hazard and exposure data and the models and approaches used. Interpretation of the risk estimates presented in this revised NMC CRA depends upon the synthesis and processing of a vast body of data on hazard and exposures. No single value in the assessment should be used to independently arrive at the interpretation of the risk estimates or results. EPA continues to have confidence -- as demonstrated by this assessment -- in the overall safety of our food supply.

Sensitivity analyses performed by the Agency were designed to evaluate the degree to which key areas of the risk assessment may or may not under- or over-

estimate the cumulative risk in an effort to characterize and understand the MOEs estimated in this assessment. The sensitivity analyses demonstrate that the Agency has not under-estimated exposures and associated risks. Also, the Agency has elected to use 10% inhibition in brain AChE as the response level for the RPFs and PoDs. The 10% response level is health protective in that no functional or behavioral effects have been noted at or below this level in adult or juvenile animals. Thus the 10% response level provides a point where functional or behavioral neurotoxicity is not expected.

The Agency has undertaken extensive risk mitigation and risk reduction efforts over the last several years for many NMCs through the single-chemical aggregate risk assessments and notes that the risk mitigation efforts of the past several years have significantly reduced risk from exposures to the NMCs through food and drinking water and from residential use in the U.S. Based on these efforts, the cumulative risks from food, water, and residential exposure to NMCs do not exceed the Agency's level of concern. Taking into account these reductions and acknowledging that several key assumptions are designed to minimize the potential for this cumulative assessment to underestimate exposure and risk, the Agency concludes that -- based on the results of the revised NMC CRA -- there is a reasonable certainty that no harm will result from exposure to the NMC pesticides covered by this assessment, taking into account the cumulative effects of such residues. Accordingly, the pesticide tolerances for the NMCs covered by this risk assessment are considered to be "safe" as defined in FFDCA section 408(b)(2)(A) and to be reassessed for purposes of FFDCA section 408(g).

LIST OF ACRONYMS

AChE	Acetycholinesterase
BMD	Benchmark dose (or **BMD_{10}**)
BMDL	Lower limit on the benchmark dose (or **$BMDL_{10}$**)
CAG	Cumulative Assessment Group
CARES	Cumulative and Aggregate Risk Evaluation System
CELs	Comparative Effect Levels
CFSAN	Center for Food Safety and Applied Nutrition
CGCM	Center for Golf Course Management
CHAD	Consolidated Human Activity Database
ChE	Cholinesterase
CMG	Common Mechanism Group
CNS	Central Nervous System
CRA	Cumulative Risk Assessment
CSFII	USDA Continuing Survey of Food Intake by Individuals
CWS	Community Water Systems
DEEM-FCID	Dietary Exposure Evaluation Model
DFR	Dislodgeable Foliar Residue
EFED	Environmental Fate and Effects Division
EFH	Exposure Factors Handbook
EPA	Environmental Protection Agency
FCID	Food Commodity Intake Database
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, Rodenticide Act
FQPA	Food Quality Protection Act
FR	Federal Register
GoF	Goodness of Fit
HCl	Hydrochloride
HED	Health Effects Division
HSRB	Human Studies Review Board
IRED	Interim Re-registration Eligibility Decision
LCO	Lawn Care Operator
LN	Lognormal
LOAEL	Lowest Observable Adverse Effect Level
LOC	Level of Concern
LOD	Limit of Detection
LOQ	Limit of Quantification
MBS	Market Basket Study
MOE	Margin of Exposure
MRID	Master Record Identification Number
NASS	National Agricultural Statistics Survey
NHANES	National Health and Nutrition and Examination Survey
NHANES III	Third National Health and Nutrition Examination Survey
NAWQA	USGS National Water-Quality Assessment Program
NHEXAS	National Human Exposure Assessment Survey
NHGPUS	National Home and Garden Pesticide Use Survey

NMC	N-Methyl Carbamate
NMC CRA	N-Methyl Carbamate Cumulative Risk Assessment
NOAELs	No-Observed-Adverse-Effect-Levels
OPs	Organophosphorus Pesticides
OP CRA	Organophosphorus Pesticide Cumulative Risk Assessment
OPP	EPA's Office of Pesticide Programs
ORETF	Outdoor Residential Exposure Task Force
ORD	Office of Research and Development
PBPK	Physiologically Based Pharmacokinetic
PCA	Percent Crop Area
PCO	Pest Control Operator
PCRA	Preliminary Cumulative Risk Assessment
PDP	USDA's Pesticide Data Program
PoD	Point of Departure
PK	Pharmacokinetic
PNS	Peripheral Nervous System
PRZM-EXAMS	Pesticide Root Zone Model- Exposure Analysis Modeling System
RBC	Red Blood Cell
RED	Re-registration Eligibility Decision
REJV	Residential Exposure Joint Venture
RPF	Relative Potency Factor
RTU	Ready-to-Use
SAP	Scientific Advisory Panel
SHEDS	Stochastic Human Exposure and Dose Simulation
SLN	Special Local Need
SOP	Standard Operating Procedure
TC	Transfer Coefficient
TDS	Total Diet Study
TTR	Turf Transferable Residues
UE	Unit Exposure
USDA	United States Department of Agriculture
USEPA	United States Environmental Protection Agency
WOE	Weight of the Evidence

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I. NMC Cumulative Update

A. Introduction

Background

The Food Quality Protection Act (FQPA) of 1996 significantly amended the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug, and Cosmetic Act (FFDCA). One of the major changes imposed by FQPA was to require EPA to consider the cumulative effects of chemicals with a common mechanism of toxicity in its tolerance reassessment decisions.

In 2001, EPA concluded that the *N*-methyl carbamate (NMC) pesticides share a common mechanism of toxicity. This common mechanism group (CMG) was established based on the shared structural characteristics and similarity and their shared ability to inhibit acetylcholinesterase (AChE) by carbamylation of the serine hydroxyl group located in the active site of the enzyme (USEPA, 2001a). For this group of pesticides, recovery typically occurs rapidly (minutes to hours) following maximal inhibition of cholinesterase (ChE). In a February 4, 2004 Federal Register notice, EPA announced the members of the Common Assessment Group (CAG) (FR Vol.69, No.23, p. 5340-5344). These ten carbamates all display ChE-inhibiting activity, have current active registrations, and are expected to contribute to the carbamate cumulative risk through quantitatively meaningful exposure scenarios. The ten members of the CAG for the *N*-methyl carbamates and those chemicals which are included in the quantitative cumulative risk assessment are listed in ive risk assessment.

Table I.A. Summary Information Regarding the NMC Pesticides and the Uses, Routes and Pathways Included in the NMC Cumulative Risk Assessment

Pesticide	Pesticide Uses	Pesticide Pathways			Pesticide Routes		
		Food	Drinking Water	Residential	Oral	Dermal	Inhalation
Carbaryl	Ag Crops	X	X		X		
	Lawn			X	X	X	X
	Garden			X		X	X
	Ornamentals			X		X	X
	Fruit Trees			X		X	X
	Pet Collar			X	X	X	
	Golfer Exposure			X		X	
Aldicarb	Ag Crops	X	X		X		
Oxamyl	Ag Crops	X	X		X		
Formetanate HCl	Ag Crops	X	X		X		
Methomyl	Ag Crops	X	X		X		
Carbofuran	Ag Crops	X	X		X		
Propoxur	Food Uses	X			X		
	Pet Collar			X	X	X	
Methiocarb	Ag Crops	X			X		
	Ornamental			X		X	X
Thiodicarb	Ag Crops	X	X		X		
Pirimicarb	Ag Crops	X			X		

To meet the requirements of FQPA, EPA developed methodologies for conducting cumulative risk assessments. As part of this process, EPA consulted with the FIFRA Scientific Advisory Panel (SAP) to obtain expert review, advice, and recommendations at each major step in the development of the underlying methodologies for cumulative risk assessments. EPA held numerous external peer-review meetings with the SAP and asked for comment on many issues, including its approaches to grouping chemicals based on a common mechanism of toxicity; Office of Pesticide Program's (OPP) guidance for conducting cumulative risk assessment; methods and approaches for dose-response and exposure assessment; and probabilistic exposure models for combining food, drinking water, and residential exposure pathways. In addition, the Agency also held numerous meetings with the FQPA Federal Advisory Committees TRAC (Tolerance Reassessment Advisory Committee) and CARAT (Committee to Advise on Reassessment and Transition), which were established under the Federal Advisory Committee Act (FACA). Various stakeholders including public interest groups, state agricultural agencies, pesticide industry representatives, growers, United States Department of Agriculture (USDA), and others were represented on these committees. In addition, numerous public technical briefings on each component of the cumulative methodology were held. In short, the Agency sought and received

advice, comments, and recommendations on the methodologies and framework that were to guide the implementation of FQPA and tolerance reassessment.

Based in part on the above consultations, OPP developed and published guidance on conducting cumulative risk assessments ("Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity") which is available on EPA's website at http://www.epa.gov/pesticides/trac/science/cumulative_guidance.pdf. This guidance has been reviewed by the FIFRA SAP and describes key principles for conducting these risk assessments. One such principle is the need to consider the time frame of both the exposure (e.g., When does exposure occur? What is the exposure duration?) and the toxic effect (e.g., What are the time-to-peak effects and the time to recovery? How quickly is the effect reversed?). Both should be adequately considered so that an individual's exposure is matched with relevant and appropriate toxicological values in terms of duration and timing. Inhibition of ChE caused by the *N*-methyl carbamates is followed by rapid recovery within minutes to hours. This rapid recovery is a unique characteristic of this group of pesticides and was considered and characterized as part of the risk assessment. Cumulative risk assessments should also account for temporal aspects of exposure, such as those related to the time of year during which applications resulting in exposures are likely to occur, the frequency of application, and the period of reapplication. Moreover, these assessments must appropriately consider age-dependent and demographic factors and patterns. The Agency's approach to each of these challenges in the cumulative hazard, exposure, and risk assessment is described throughout the document.

This cumulative assessment is intended to identify major sources of risk that could potentially accrue due to the use of a variety of pesticides which act through a common mechanism of toxicity. Regulatory decision making is based on the many detailed aspects of the single-chemical aggregate risk assessment. Because of the requirement that many data sets be combined into a single assessment, reducing the impact and likelihood of compounding conservative assumptions and over-estimation bias becomes very important in constructing the cumulative risk assessment. As a result, OPP has chosen to work with those data that most closely reflect likely exposures and not to incorporate those data that are inherently conservative by their nature (e.g., field trial data which incorporate maximum application rates and minimum pre-harvest intervals). These principles are fully described and laid out in the aforementioned guidance document.

EPA previously released the "Estimation of Cumulative Risk from *N*-methyl Carbamate Pesticides: Preliminary Assessment" in August 2005. During the period since the issuance of the preliminary cumulative risk assessment, the Agency has been working to further improve and refine its assessment of the cumulative risks associated with the NMC pesticides. These refinements

include changes to: incorporate the most recent food residue data by including pesticide residue data through 2006 from USDA's Pesticide Data Program; reflect the Agency's review of new toxicity data in juvenile animals; and to incorporate human data for certain NMC pesticides. In addition, the Agency has updated the assessment to reflect individual risk mitigation measures and other use pattern changes for individual NMC pesticides since the preliminary NMC CRA was issued in August 2005. Specifically, during this period, the Agency imposed risk reduction measures on some of the major contributors to carbamate cumulative risk, as discussed below. The risk estimates presented in the revised NMC CRA reflect the risk mitigation measures taken on individual carbamates since FQPA was signed into law in August 1996. A table summarizing these mitigation measures is provided in Appendix II.A. In general, EPA's risk estimates reflect risk mitigation measures that EPA determined to be warranted based on its assessment of the single chemical's risks. For all of the risk mitigation measures that are reflected in this document, EPA has commenced the processes necessary to implement its selected risk mitigation, but may not yet have completed these processes. Having already determined that risk mitigation is warranted for the individual chemical, EPA has chosen to exclude it from this assessment to avoid any confusion that yet further mitigation might be warranted solely on that basis, either for the individual chemical or for other NMC chemicals. Rather, where the risks are adequately addressed by previously identified risk mitigation, it was considered to be unnecessary to confirm that here. To the extent that any risk mitigation measures are not subsequently implemented as envisioned in this assessment, the revised NMC CRA will be revised as necessary. The following summarizes the major mitigation actions that the Agency has recently or will be taking with respect to registration of uses which have been excluded from the revised NMC CRA:

Carbofuran. In July 2006, the Agency issued its proposed decision to cancel all domestic uses of Carbofuran; only four import tolerances, (coffee, bananas, sugarcane, and rice) would remain. A Federal Register (FR) notice announcing this decision and soliciting public comments was published on August 30, 2006.

Any cancellation hearing for EPA's proposed decision on carbofuran would be scheduled to commence in 2008, which is after the issuance of this document. If all remaining uses of carbofuran are not cancelled after conclusion of a cancellation hearing, this assessment will be revised as necessary.

Methomyl. The methomyl registrant submitted a letter requesting the voluntary cancellation of the strawberry use on January 4, 2007. A Federal Register notice announcing the receipt of this request to delete the methomyl strawberry use published on April 25, 2007 (72 FR 20541) (FRL-8125-6). The public comment period for this notice closes on October 22, 2007.

A letter requesting voluntary cancellation of the use of methomyl on grapes was received from the registrant on September 14, 2007. A Federal Register notice announcing the receipt of this request will be published in October 2007. Based on these voluntary cancellations, the use of methomyl on grape and strawberry has been excluded from the *N*-methyl carbamate cumulative risk assessment.

Propoxur. In February 2007, the propoxur registrant submitted a letter requesting the voluntary cancellation of the all indoor spray uses that may result in non-occupational exposure for children. A Federal Register notice announcing this voluntary cancellation and soliciting public comments was published on April 25, 2007 (72 FR 20541) (FRL-8125-6). In July 2007, the Agency issued its Final Use Termination Order for Propoxur Residential Spray Use (EPA Registration Number 432-1288) for the use of propoxur, when formulated into a product that can be used as a spray on residential indoor use sites. The Agency has evaluated *N*-methyl Carbamate cumulative risks in a manner that *excludes* these crack and crevice-type residential uses so as to reflect the Agency's final termination order.

Aldicarb. In September 2007, EPA completed the Aldicarb Reregistration Eligibiility Decision (RED). The Agency identified potential human health risks of concern associated with the current registered uses of aldicarb from drinking water exposure, and potential environmental risks of concern to birds, mammals and fish. To reduce these potential exposures and to address current risks of concern, EPA -- in agreement with the technical registrant of aldicarb -- will implement certain label restrictions. To address groundwater contamination concerns, the Agency will increase drinking water well set-backs for applications to peanuts in the southeastern coastal plains when certain criteria are triggered. In addition, to reduce environmental concerns, the Agency will implement application rate reductions and restrictions, state limitations, label amendments, and cancellation of certain commodities. EPA is also requiring data to confirm the decisions presented in the Aldicarb RED which and will seek public comment on the decisions in the RED in October 2007.

The current document is presented in three major parts:

- Part I: Revised NMC Cumulative risk assessment

- Parts II and III: Appendices which provide background material, additional graphs, and more technical and/or extensive details surrounding the analyses contained in Part I

Part I is divided into eight chapters. Chapter A is this general introduction. The following chapter (I.B), presents the Hazard Assessment with specific discussion of the Relative Potency Factor approach and empirical dose-response and time course modeling used to estimate relative potency. The next three chapters (C, D, and E) focus on each of the major exposure pathways (food, residential, and drinking water, respectively), including a discussion of assumptions, data inputs, and interrelationships of exposure data. Each of these pathways has unique issues relating to availability of data, scale, and interpretation of results. Results of each aspect of the assessment are discussed in these chapters with particular attention given to how they reflect potential exposures to the population and what might be inferred with regard to significant exposure pathways/scenarios. Chapter F of the document examines the results of combining estimates of risk from all sources of exposure, in a multi-pathway, probabilistic cumulative assessment, and further discusses the interpretation of the outputs with respect to the most significant pathways and scenarios. The results in this chapter were generated by the DEEM/Calendex software. Chapter G of this document is a risk characterization, which further discusses and characterizes the inputs to the assessment as well as the resulting model exposure estimates. Chapter H of this document provides references for the material cited in Parts A through G.

B. Hazard Relative Potency Factors

1. Introduction

OPP designated the NMC pesticides as a common mechanism group (USEPA, 2001a) based on the shared structural characteristics and similarities and their shared ability to inhibit AChE by carbamylation of the serine hydroxyl group located in the active site of the enzyme. Following maximal inhibition of cholinesterase, recovery typically occurs rapidly (minutes to hours). Pharmacokinetic data are only available for one NMC (i.e., carbaryl), Consequently, a multi-chemical, multi-pathway physiologically based pharmacokinetic (PBPK) model cannot be developed at this time for the NMC cumulative risk assessment (Appendix II.B.6). Therefore, the 2007 revised cumulative risk assessment relies on the relative potency factor (RPF) method for quantifying chemical potency. In the RPF approach, the toxic potency of each chemical is determined. A member of the cumulative assessment group (CAG) is selected as the index chemical which is used as the point of reference for standardizing the cholinesterase inhibiting potency of the other chemical members of the CAG. In the case of the NMC CRA, oxamyl is used as the index chemical.

The FIFRA SAP supported the scientific approach employed in the NMC cumulative hazard in the February and August 2005 meetings. EPA has considered the comments collected from the SAP as well as the registrants' error-only comment phase in July 2005 in the development of the current revised NMC CRA. The revised NMC CRA incorporates additional data available since the 2005 preliminary CRA in addition to uncertainty factors for the inter- and intra-species factor and FQPA 10X safety factor. Specifically, the Agency has included comparative cholinesterase data in juvenile (post-natal day 11 [PND 11] and PND17) and adult rats for six chemicals as well as cholinesterase inhibition and recovery data from human subjects for three chemcials. The comparative cholinesterase data are used here to inform the FQPA 10X factors while the cholinesterase data in human subjects has been used to form the inter-species factor in the revised CRA. It is noted that carbofuran has been ruled ineligible for reregistration and is undergoing the process of cancellation. However, for completeness and because tolerances for bananas, coffee, rice and sugarcane will continue for import purposes, the hazard chapter includes RPFs and uncertainty factor information for carbofuran.

This cumulative hazard assessment represents the collaborative efforts of scientists from OPP and EPA's National Health and Environmental Effects Research Laboratory (NHEERL) and National Center for Computational Toxicology (NCCT). The purpose of this hazard chapter is to describe EPA's approach for:

- Determination of the relative cholinesterase inhibiting potency and half-life to recovery used for each *N*-methyl carbamate in the CAG;
- Selection of the index chemical used as the point of reference to standardize the potency of each *N*-methyl carbamate;
- Establishment of a baseline or reference value (i.e., points of departure) used to estimate potential risk for the group for each route of interest; and
- Identification of the intra-species, inter-species, and FQPA 10X safety factors used in this cumulative risk assessment.

2. Endpoints and Toxicology Studies

When using the RPF method and before the cumulative risk of exposure to the NMCs can be quantified, the relative toxic potency of each NMC must first be determined. The determination of relative toxic potency is calculated using a uniform basis of comparison, by using, to the extent possible, a common tissue, species, and sex for all the exposure routes of interest (USEPA, 2002a). NMCs exert their neurotoxicity by carbamylating the enzyme acetylcholinesterase (AChE) in both the central (brain) and peripheral nervous systems. Since cholinesterase (ChE) inhibition is the critical event in NMC toxicity, ChE inhibition provides the common endpoint for the revised NMC CRA. The available ChE activity measures provide a more uniform measure of toxicity compared to behavioral measures for performing cumulative risk assessment. Behavioral measures are often limited in terms of the scope of effects assessed and by the lack of standardization of laboratory equipment among laboratories. Moreover, behavioral changes in animal studies usually occur at similar or higher doses compared to doses needed to inhibit cholinesterase activity. In order to evaluate the concordance between ChE inhibition and behavioral endpoints, EPA has performed a series of dose-response and time course studies with seven NMCs where RBC and brain ChE, along with clinical signs ('tox' score) and motor activity, were measured (Appendix II.B.5; McDaniel *et al.*, 2007; Padilla *et al.*, 2007).

There are laboratory animal data on NMCs for cholinesterase activity in plasma, red blood cell (RBC), whole blood, and brain (whole brain and brain sections). Measures of ChE inhibition in the peripheral nervous system (PNS) are very limited for ChE inhibiting pesticides, in general. As a matter of science policy, blood cholinesterase data (plasma and RBC) are considered appropriate surrogate measures of potential effects on PNS acetylcholinesterase activity, and of potential effects on the central nervous system (CNS) when brain ChE data are lacking (USEPA, 2000a). Furthermore, when RBC ChE data are of adequate quality, as is the case for the NMCs, RBC ChE data are preferred over plasma ChE data. AChE is the target enzyme for this common mechanism group and is the primary form of ChE found in RBCs.

Butylcholinesterase (BChE) is the primary form found in plasma. Inhibition of BChE is considered a measure of exposure, but has not been shown to be of toxicological significance. Some studies with NMCs provided whole blood ChE. Whole blood ChE represents a mixture of plasma and RBC ChE, and thus may not provide a uniform endpoint for comparison across chemicals. Consequently, whole blood ChE data were not used in this assessment. In the case of brain ChE inhibition, data are available for each NMC with whole brain (or half brain). In some studies, brains were dissected into different brain areas (e.g., cerebellum). Because the brain dissections provided are not standardized across the studies and brain section data are not available for each NMC, these data do not represent a uniform basis of comparison. RBC and brain (namely whole, half) ChE inhibition were considered potential endpoints for extrapolating risk to humans in the revised NMC CRA. **As described in Section B.4 below, the Agency is using brain ChE data as the basis for RPFs and points of departure (PoD) in this assessment.**

Humans may be exposed to the NMCs through food and drinking water and in and around residences, schools, commercial buildings, etc. Therefore, the potency of NMCs needs to be determined for the oral, dermal, and inhalation routes of exposure. Under FIFRA, toxicity studies in various species (e.g., dog, mouse, rat, and rabbit) are submitted to OPP. For the NMCs, toxicity studies in the rat provide the most extensive and robust database of ChE inhibition data. Thus, the focus of this analysis was on ChE activity data derived from male and female (non-pregnant) rats. EPA used rabbit studies for pesticides with residential/non-occupational exposure potential when dermal toxicity data in rats were not available.

Toxicological characteristics of the NMCs involve maximal ChE inhibition followed by the rapid recovery, typically in minutes to hours. As such, the critical duration of exposure for this common mechanism group is acute ChE inhibition measured at the peak time of effect. Characterizing chemical specific recovery is critical for characterizing overlapping exposures and thus cumulative risk. EPA has compiled data from several different kinds of studies:

1. oral (gavage) studies quantifying the relationship between maximum inhibition from single or multiple administered dose(s) in adult rats;

2. oral (gavage) studies quantifying the *in vivo* recovery time course, usually at several doses, and beginning at or around the time of maximum inhibition (which had typically been determined in preliminary studies) in adult rats;

3. comparative cholinesterase assay (CCA) studies quantifying the ChE sensitivity of juvenile rats compared to adult rats; comparing dose-response and time to recovery in juvenile (PND11 and/or PND 17) and adult rats; and/or

4. oral double blind ascending studies quantifying the dose-response and recovery time course of ChE in humans; and,

5. inhalation and dermal studies for those pesticides with residential exposure.

Data included in the revised NMC CRA were extracted from studies submitted by pesticide registrants and from dose-response and time course studies performed by EPA's NHEERL. Table I.B-1 provides the list of various types of studies included in the analysis. Appendix II.B.1 contains the electronic spreadsheets of brain and RBC ChE data used.

Table I.B-1. Test guidelines/studies that contain evaluations for ChE activity.

Study Type	Guideline Type
Oral	
Acute oral toxicity study in rat	OPPTS 870.1000
Acute neurotoxicity in rat	OPPTS 870.6200a
Subchronic neurotoxicity in rat	OPPTS 870.6200b
Developmental neurotoxicity oral in rat	OPPTS 870.6300
Chronic oral toxicity in rat	OPPTS 870.4100
Range finding oral toxicity study in rat	Not applicable
Other/Special Studies	Not applicable
Dermal	
21/28-Day dermal toxicity in rat or rabbit	OPPTS 870.3200
Inhalation	
Acute inhalation in rat	OPPTS 870.1200
Chronic inhalation in rat	OPPTS 870.4100

In toxicology studies submitted to EPA for pesticide registration, measurements of cholinesterase inhibition are typically performed using some variation of the Ellman spectrophotometric method (Ellman *et al*., 1961). Under standard conditions, this method usually involves extensive sample dilution, prolonged incubation, and temperatures around 37°C; all of which promote reversal of the enzyme inhibition. If precautions are not taken to prevent

recovery using this method, then reported cholinesterase activities can underestimate actual cholinesterase inhibition (Winteringham and Fowler, 1966; Williams and Casterline, 1969; Nostrandt *et al.*, 1993; Hunter *et al.*, 1997) which could have an impact on the relative potency estimates. A radiometric method such as that reported by Johnson and Russell (1975) provides the most appropriate method for measuring cholinesterase inhibition due to NMC exposure because factors which promote reversibility are minimized. The dilution is minimized (1:30 vs. more than 1:1000 dilution for the standard Ellman method), and incubation time may be more rapid for the radiometric method (one to three minutes compared to 10 minutes or greater). Furthermore, the radiometric method may be conducted at lower temperatures. The Ellman method can be modified to minimize conditions promoting reactivation. Reducing the tissue dilution, shortening the time, and lowering the temperature of the assay all limit the amount of spontaneous decarbamalyation of the inhibited enzyme (Nostrandt *et al.*, 1993). Although modifications to the Ellman method are not standardized, when performed with the appropriate care, the modified Ellman method can provide reliable cholinesterase data.

To aid in the characterization of the cholinesterase data provided by the studies submitted for registration, scientists from EPA's NHEERL have systematically evaluated cholinesterase inhibition following acute exposures of adult rats to seven *N*-methyl carbamates (carbaryl, carbofuran, formetanate HCl, methomyl, methiocarb, oxamyl and propoxur) using both the standard Ellman and radiometric techniques. This work has been published in the scientific literature (Padilla *et al.*, 2007); the data from these experiments are also included in Appendix II.B.1. EPA's issue paper presented to the FIFRA SAP in February, 2005 provided graphical comparisons of the data from selected registration studies and EPA's radiometric experiments. These graphical comparisons showed good concordance between the registration data and EPA's radiometric experiments. In the current revised cumulative risk assessment, these data have been analyzed statistically (see section I.B.3). Overall, the results provided by the EPA radiometric studies provide similar benchmark dose estimates to the registration studies.

The laboratory protocols or standard operating procedures (SOPs) for some registration studies have been provided by the pesticide registrants. EPA has received protocols or SOPs for studies for nine of the ten NMCs. Methiocarb is the only chemical the Agency has not received a protocol or SOP for measuring cholinesterase activity. The protocols available indicate that the experimental conditions among laboratories vary but that dilutions are generally limited to approximately 1:20 and that samples are frozen immediately. Although information regarding the time of sample handling is more limited, the available information suggests that reasonable precautions were taken in these studies to reduce reactivation prior to analysis. The Agency considers the methods used to evaluate ChE activity in the laboratory to be a critical component of the hazard assessment for the NMCs and will continue to

evaluate SOPs as new studies are submitted in the future. A summary of the information provided in these protocols can be found in Appendix II.B.5.

A summary of the studies and endpoints included in the revised cumulative risk assessment for the NMCs are provided in Table Table I.B-2. This table includes studies recently submitted, such as comparative cholinesterase studies and human studies reviewed and found to be ethically conducted and scientifically valid by the Human Studies Review Board (HSRB) in 2006.

Table I.B-2. List of toxicity studies used in the Revised *N*-Methyl Carbamate Risk Assessment.

Chemical	Oral		Dermal		Inhalation	
	Study ID	ChE Inhibition Data	Study ID	ChE Inhibition Data	Study ID	ChE Inhibition Data
Aldicarb	43442305[1]	Brain, RBC	No residential uses, thus data are not needed			
	43442302[2]	RBC				
	45079705	RBC				
	43829601	Brain, RBC				
	43829602	Brain, RBC				
	45068601[3] 45150701 46618001	Brain				
	42373001	Human RBC				
Carbaryl	43845202	Brain, RBC	45630601 (47151902)	Brain, RBC (In vitro dermal penetration)	Inhalation data are not available	
	43845203	Brain, RBC				
	44122601	Brain, RBC				
	44393701	Brain, RBC				
	47007001/ 47143001	Brain, RBC (NHEERL CCA)				
	NHEERL Padilla et al., 2007	Brain, RBC				
	NHEERL 47143001	Brain, RBC comparative				
Carbofuran	45675701	RBC	No residential uses, thus data are not needed			
	46688912-14	CCA Brain				
	47143703-05	CCA Brain, RBC				
	Moser CCA	Brain, RBC				
	Padilla et al., 2007	Brain, RBC				
Formetanate	46618901	CCA Brain, RBC	No residential uses, thus data are not needed			
	Padilla et al., 2007	Brain, RBC				
Methiocarb	Padilla et al., 2007	Brain, RBC	40922301	Brain, RBC	Data are not available	
			41771701	Brain		
Methomyl	44472001	Brain, RBC	No residential uses, thus data are not needed			

	Oral		Dermal		Inhalation	
	44487501	Brain, RBC				
	46646401	CCA Brain, RBC				
	Padilla et al., 2007	Brain, RBC				
	44721401	Human RBC				
Oxamyl	44254401	Brain, RBC	40827601	Brain, RBC	45155801	Brain, RBC
	44472001	Brain, RBC				
	44420301	Brain	44751201			
	46615301	CCA Brain, RBC				
	Padilla et al., 2007	Brain, RBC				
	44912301	Human RBC				
Pirimicarb	44485301	Brain, RBC	No residential uses, thus data are not needed			
	44233103	RBC				
	00113638	Brain, RBC				
Propoxur	Padilla et al., 2007	Brain, RBC	41066001	Brain, RBC	42648001	Brain, RBC
Thiodicarb	45138702	RBC	No residential uses, thus data are not needed			
	45138703	Brain, RBC				

[1]Brain and RBC data for parent only used in the analysis; [2] Brain data at 24 hours not used in the analysis; [3]MRIDs listed here are referenced in the Aldicarb oral rat brain ChE analysis in Appendix II.B.2 as: 1) 46618001 as Moser-1; 2) 45068601 as Moser-2; and 3) 45150701 as Moser-3.

3. Determination of Toxic Potency

As described in the guidance document for cumulative risk assessment (USEPA, 2002a), dose-response modeling is preferred over the use of NOAEL/LOAELs (i.e., no- or lowest-observed-adverse-effect-levels) for determining relative toxicity potency. NOAELs and LOAELs do not necessarily reflect the relationship between dose and response for a given chemical, nor do they reflect a uniform response across different chemicals. In the present analysis, benchmark dose (BMD) modeling has been used to determine the toxic potency of the NMCs. EPA's draft BMD guidance (USEPA, 2000d) suggests that the central estimate on the BMD provides an appropriate measure for comparing chemical potency and that the lower limit on the central estimate (i.e., BMDL) provides an appropriate measure for extrapolating risk. The 10% response level is generally at or near the limit of sensitivity for discerning a statistically significant decrease in ChE activity across the blood and brain compartments and is a response level close to the background ChE. As part of EPA's Revised Cumulative Risk Assessment for the OPs, EPA performed a power analysis of brain ChE data available for more than 30 OPs (USEPA, 2002b). The results of the analysis indicated that most studies can reliably detect 10% brain ChE inhibition. Furthermore, in studies submitted to EPA for pesticide registration, clinical signs and behavioral effects have not been shown in studies with below 10% ChE inhibition. In this cumulative risk

assessment, the central estimate of the BMD_{10} was selected as the response level for developing RPFs. The lower limit on the BMD_{10} (i.e., $BMDL_{10}$) was selected for the points of departure (PoDs). A PoD is a point estimate on the index chemical's dose-response curve that is used to extrapolate risk to the exposure levels anticipated in the human population.

The following section describes the empirical dose-response modeling performed for the NMCs. BMD_{10} and $BMDL_{10}$ estimates for the NMCs are provided in Tables 1.B-3 thru 5. Half-life time to recovery for each of the NMCs is provided in Table 1.B-6. Detailed information about the empirical modeling for each chemical can be found in Appendix II.B.2.

a. Empirical Modeling: Dose-Time Response Model and Benchmark Dose Estimation

i. Dose-Time Response Model

Several features of the dose-time response for the *N*-methyl carbamates were to be captured in an empirical model:

- The rapid decline of ChE activity with increasing dose, perhaps after a "shoulder" at the low-dose end of the dose-response curve;
- A potential minimum level below which ChE activity will not drop, regardless of dose;
- The rapid decline of ChE activity after dosing to a minimum level which depends upon dose, then returns to the background level over a period of minutes to hours, at a rate that may also depend upon dose;
- Lack of early time points in most of the time course studies to accurately estimate the time of maximum effect, but instead start collecting data around a previously estimated time of maximum effect.

The model described is the result of multiplying a dose-response model for inhibition that is closely related to the model that was successful at characterizing OP dose-response curves (USEPA, 2002b) and a time-course model for inhibition. Transformations of parameters were used to enforce constraints, since the statistical software used for estimating model parameters does not incorporate bounded estimation (for example, to require that half-life estimates remain positive).

The model for inhibition, before parameters were transformed to enforce constraints, is

$$g(d) = g(d; R, P, D_R, \gamma) = (1-P)\left(1 - e^{\log\left(\frac{1-R-P}{1-P}\right)\left(\frac{d}{D_R}\right)^{\gamma}}\right)$$

(Eq. 1)

where:

- d is administered dose, and is part of the data set;
- P is the minimum fraction of background ChE activity, and is constrained to fall between 0 and 1;
- R is the inhibition fraction associated with the desired benchmark dose (that is, the benchmark dose is the dose expected to yield 100×R% inhibition at the time of maximum effect), and is set to 0.10 in this analysis;
- D_R is the benchmark dose, constrained to be greater than 0.0;
- γ is a shape parameter to allow a shoulder at the low-dose end of the dose-response curve, and is constrained to be greater than 0.0.

Two different time course models were used. One time course model is the difference of two exponential functions, scaled so that the maximum is always 1:

$$h(t) = h(t; T_A, T_R) = C_0\left(e^{-\frac{\ln(2)t}{T_R}} - e^{-\frac{\ln(2)t}{T_A}}\right)$$

(Eq. 2)

where:

- T_A is the half-life of the process that results in an increase in inhibition, and
- T_R is the half-life of the process that results in a decrease in inhibition (recovery or reactivation).

The maximum of *h(t)* occurs at:

$$T^* = \frac{T_R T_A \left(\ln\left(T_R\right) - \ln\left(T_A\right)\right)}{\ln\left(2\right)\left(T_R - T_A\right)}$$

(Eq. 3)

so

$$C_0 = 1 \Big/ \left(e^{-\frac{\ln(2)T^*}{T_R}} - e^{-\frac{\ln(2)T^*}{T_A}} \right)$$

With this scaling, h(t) is symmetric in the two parameters (that is, *h(t; a, b)* = *h(t; b, a)*), which complicates statistical estimation unless a constraint is added to keep $T_R > T_A$. Also, many data sets require that T^* be specified (not estimated from the data), because the designs were inadequate for estimating T^*. For these reasons, it is convenient to reparameterize the model in terms of T^* and $\alpha = T_R / T_A$ and make sure α is constrained to be greater than 1.0.

The design of most of the time-course datasets considered in this assessment did not allow clean estimation of both T^* and α, and the reparameterization sometimes increased the difficulty of estimation. Thus, an alternative, much simpler, time-course model was used in all but one of the dose-time studies (aldicarb, brain ChE). In this simpler model, ChE activity is taken to be described by an exponential recovery time-course, beginning at a time δ after dosing. This gives the following recovery function:

$$h(t) = e^{-\frac{\ln(2)(t-\delta)}{T_R}}$$

(Eq. 4)

where:
T_R is the half-life of recovery
δ is the difference in time between dosing and the first ChE measurement.

In this model, the only parameter to be estimated is T_R.

Multiplying *g(d)* and *h(t)* together gives a function for ChE inhibition as a function of dose and time. Thus, Equation 5

$$f(t, d) = A \times (1 - g(d) \times h(t))$$

is a model for ChE activity as a function of dose and time, where *A* gives the background (that is, control) level of ChE activity.

There were no time-course data for any of the dermal and inhalation data sets, so the above model was simplified for those sets, either by setting the time course parameters to a fixed value, or by fitting a linear model to the natural logarithm of ChE activity, which is equivalent to an exponential dose-response model when the variance is proportional to the square of the mean ChE activity level (that is, the coefficient of variation is constant across doses).

The following transformations were used to ensure that parameters remained in their permitted range:

- $lA = ln(A)$, to force $A > 0$
- $lD = ln(D_R)$, to force $D_R > 0$
- $tz = -ln((1 - R - P)/P)$, to force $0 < P < 1 - R$
- $lg = ln(\gamma)$, to force $\gamma > 1$
- $lTr = ln(T_R)$, to force recovery half-life > 0 (in simplified time-course model)
- $ldT = ln(\alpha)$, to force $T_R > T_A$
- $lT_{max} = ln(T_{max})$, to force $T_{max} > 0$.

ii. Statistical Methodology

The statistical model fit to the dose or dose-time response data depended on whether the experimental design involved repeated measures (some RBC studies only) or not. The most general model fit to the ChE activity data was (for the simplified time course model), for individual j in study i, with sex $s(j)$ at time t_{ijk}:

$$y_{ijk} = f(t_{ijk}, d_{ij}; lA_{is(j)jk}, lD_{is(j)}, tz, lg, lTr_{is}, delta) + \varepsilon$$
$$\varepsilon \sim N\left(0, \sigma^2_{is(j)} \{f(\cdots)\}^q\right)$$

When there was more than one study,

$$lD_{is(j)} \sim N\left(lD_{s(j)}, \sigma^2_D\right),$$

that is, the log BMD was taken to be normally distributed around a mean that possibly differed between sexes.

When there were repeated observations on a subject, the logarithm of individual animals background ChE activity levels were assumed to be normally distributed about a mean that varied between sexes, studies, and, when there were controls at all times, among times (this latter allows for the possibility of variation among analytic batches, if samples from the same time post dosing were analyzed as a batch).

$$lA_{is(j)jk} \sim N\left(lA_{is(j)k}, \sigma_A^2\right),$$

When recovery time-course data were available, the recovery half-life was allowed to differ among the doses for which recovery data were available. Often for a chemical, some datasets were just dose response studies conducted around the time of maximum inhibition, and others included a recovery phase, with samples taken every few hours or more frequently. In this case, the range of doses in all the studies together was grouped so that one dose with a time-course was included in each group. This allowed the estimate of recovery half-life to change with dose when the right data were available. However, often a chemical had recovery time course data for only a single dose level, so only a single recovery half-life could be estimated.

The process of estimating parameters proceeded in three steps. First, initial values for the parameters were arrived at using the R function getInitialValues (included in the library DRUtils). This function provides a graphical interface that allows the user to quickly arrive at reasonable estimates for the parameters, and allows a few iterations of an optimization algorithm to improve those initial estimates, using ordinary least squares as an objective function. Based on these initial estimates, the degree to which it would be possible to uniquely estimate the model parameters was determined, by analyzing the condition number of the matrix of gradient of the model with respect to the model parameters, and of the matrix of (unscaled) variances and covariances of the parameters, evaluated at the data points (times, doses, sexes) in all the data sets. At this point, it was often possible to simplify the model by noticing that it was impossible to determine a unique value for, for example *tz*, because doses did not go high enough for inhibition to approach its maximum value, or the maximum level of inhibition was 100%.

The next step was to determine an appropriate model for the error variance. The options considered were either; a constant variance, a constant

variance that differed among studies and sexes, or a variance that was proportional to a power of the mean ChE activity level, and whose constant of proportionality varied among studies and between sexes. This was determined by fitting either a cell mean model (with indicator functions identifying individual dose X time X sex X study groups) or, more commonly, fitting the full nonlinear dose-time model using generalized nonlinear least squares (Pinheiro and Bates, 2000). In either case, likelihood ratio tests were used to identify the variance model to use (Pinheiro and Bates, 2000).

Using that variance model, a full version of the dose-time course model was fit to the data, and contrasts used to determine whether *ID* needed to differ among sexes. Pinheiro and Bates (2000) note that likelihood ratio tests for fixed effects in mixed effects models tend to reject the null hypothesis enthusiastically, whereas using contrasts to test parameter values comes close to the nominal type I error rates.

Finally, a simplified model was fit to the data, and the resulting parameter estimates used to determine the values of *ID* and *ITr* and their standard errors. BMDs were calculated as exp(*ID*), and BMDLs were calculated by exponentiating the lower end of a two-sided 90% confidence interval for *ID*.

All statistical analyses used the statistical software environment R (version 2.0.1, patched version of 2005-01-26; R Development Core Team, 2004) and its associated packages. Appendix II.B.3 contains the computer code used in EPA's analyses.

b. Results: Benchmark Dose and Potency Estimation

Results of the empirical dose-response modeling are provided below. Detailed descriptions of the analysis and results of empirical dose-response modeling for each chemical are provided in Appendix II.B.2.

The oral BMD_{10}s for the NMCs range across several orders of magnitude with aldicarb and pirimicarb representing the most and least potent pesticides, respectively, for both brain and RBC ChE inhibition. The number of studies available for analysis varies among the chemicals (Table 1. B-2). At least two studies containing RBC and whole brain ChE inhibition in male and female rat were available for eight of ten NMCs (aldicarb, carbaryl, carbofuran, formetanate HCL, oxamyl, methomyl, pirmicarb, and thiodicarb). At present time, the only RBC and whole brain ChE data for methiocarb and propoxur are from EPA's NHEERL dose-response and time course studies in male rats (Padilla *et al.*, 2007).

For those chemicals that have data in male and female adult rats, EPA analyzed both sexes. When male and female data provided statistically similar BMD_{10}s, the data were combined and analyzed jointly. This joint analysis

provides a more robust analysis using all the available data. In cases where the BMD estimates were statistically different, sex specific BMD_{10}s are presented (Table I.B-3, and Table 1.-5, below). As mentioned above, only male data are available for two NMCs (methiocarb, propoxur). Reliable BMD_{10} estimates for RBC ChE inhibition from pirimicarb could not be calculated due to a lack of response even at the highest doses tested (110 mg/kg).

ChE inhibition measured using both radiometric and modified Ellman techniques are available for aldicarb, carbaryl, carbofuran, formetanate HCl, methomyl, and oxamyl. RBC and brain ChE data from the two methods provided statistically similar BMD_{10} estimates for all of the chemicals and were combined in the analysis to provide a more robust potency estimate. As shown in Table I.B-3, for carbaryl, both methods provided similar BMD_{10} estimates for RBC ChE. However, for brain ChE in males, the BMD_{10} estimated from EPA's radiometric study is larger than that estimated from the studies using modified Ellmans. Four registration studies were included in the analysis (MRID nos. 43845202, 43845203, 44122601, 44393701). For all four studies, Sprague-Dawley rats were administered via gavage with an aqueous vehicle of 0.5% (w/v) carboxymethyl-cellulose (high viscosity)/0.1% (w/v) Tween 80 (10mL/kg). EPA's experiments involved Long Evans rats dosed via gavage with corn oil (1 mL/kg) as the administration vehicle. Given that each of the carbaryl studies provided valid and acceptable ChE data, there is no scientific support for removing any studies from the analysis. Thus, the Agency has decided to include all the available brain ChE data in the carbaryl BMD_{10} estimate used for potency determination (i.e., registration combined with Padilla data of 1.6 mg/kg).

Table I.B-3. Oral BMD_{10}s and $BMDL_{10}$s from rat brain and RBC ChE inhibition for the *N*-methyl carbamates

Chemical	Brain		RBC	
	BMD_{10} (mg/kg)	$BMDL_{10}$ (mg/kg)	BMD_{10} (mg/kg)	$BMDL_{10}$ (mg/kg)
Aldicarb	F= 0.05 M= 0.06	F= 0.03 M= 0.03	0.03	0.02
Carbaryl	Registration F= 1.60 Registration M= 1.21 NHEERL M=5.46 Combined M=1.58 Moser = 2.63	Registration F= 1.35 Registration M= 0.99 NHEERL M= 4.15 Combined M= 1.11 Moser = 2.03	Reg. =5.59 Moser = 0.96	Reg. = 3.41 Moser = 0.73
Carbofuran[2]	0.10	0.0873	0.03	0.01
Formetanate HCl[2]	0.11	0.06	0.09	0.03
Methiocarb[2]	1.31	0.56	3.18	0.81
Methomyl	0.36	0.2677	0.20	0.11
Oxamyl	0.24	0.18	0.28	0.16
Pirimicarb	11.96	6.98	NA	NA
Propoxur[2]	2.09	0.83	1.54	0.28
Thiodicarb	0.27	0.23	1.39	0.90

[1]BMD estimates are presented as a single estimate when there are no differences between sexes and between the radiometric and modified Ellman methods, unless otherwise noted.
[2]BMD estimates are for male only
NA: No relationship between RBC ChE activity and pirimicarb dose.

Figure I.B-1. Plot of BMD_{10}s and the 95% confidence limits for rat brain ChE inhibition for the *N*-methyl carbamates

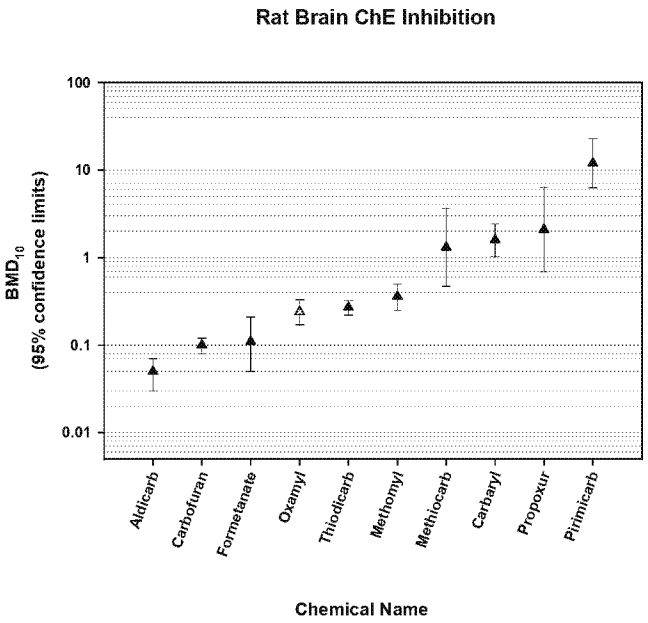
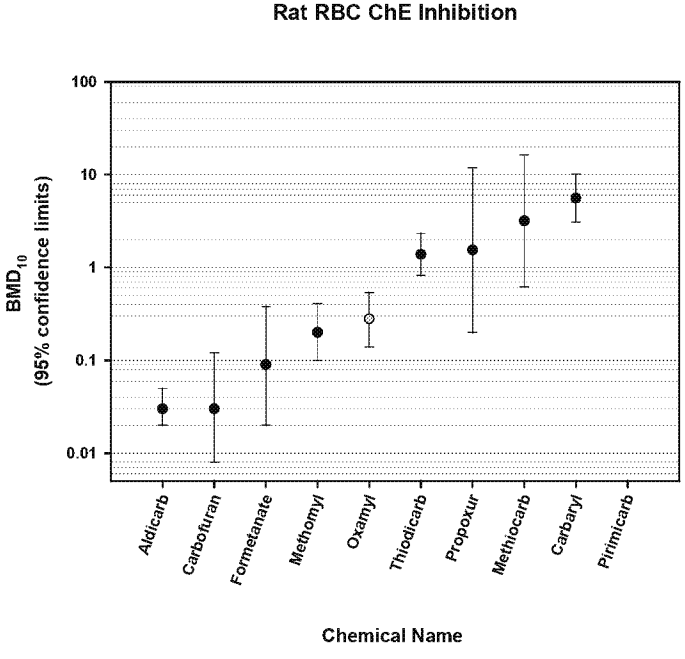


Figure I.B-2. Plot of BMD_{10}s and the 95% confidence limits for rat RBC ChE inhibition for the *N*-methyl carbamates[1]



[1]BMD_{10}/ $BMDL_{10}$ for RBC ChE were not developed for pirmicarb; no dose-response relationship was observed up to highest dose tested (110 mg/kg).

Potency estimates (BMDs) used for calculating dermal and inhalation RPFs are provided in Tables 1.B-4 and 1.B-5. Dermal and inhalation RPFs are needed for carbaryl, methiocarb, and propoxur as these have residential uses. Sufficient dose-response data were available for carbaryl to calculate BMD_{10} estimates for RBC and brain ChE via the dermal route. As for the dermal

studies with methiocarb and propoxur, no ChE inhibition was observed up to the highest doses tested. The highest doses in the methiocarb and propoxur studies have been used to estimate dermal relative potency.

Table I.B-4. Dermal BMD_{10}s, $BMDL_{10}$s, and potency estimates from rat and rabbit brain and RBC ChE inhibition for the *N*-methyl carbamates with residential/non-occupational uses[1]

Chemical	Brain		RBC	
	BMD_{10} (mg/kg)	$BMDL_{10}$ (mg/kg)	BMD_{10} (mg/kg)	$BMDL_{10}$ (mg/kg)
Carbaryl[2]	49.35[3]	30.56	F= 86.18 M= 59.04	F= 60.55 M= 46.91
Methiocarb[4]	375[5]			
Propoxur[4]	1000[5]			

[1] See Table I.B.7 for brain BMD_{10}s and $BMDL_{10}$s for oxamyl; [2]Data from rat studies; [3]Comparative In vitro dermal penetration data were NOT used to refine the brain BMD; [4]Data from rabbit studies; [5]Dermal endpoint is based on the highest dose tested in the dermal study; No ChE inhibition was observed at any dose.

Rat inhalation data with propoxur were available to estimate a BMD_{10} for brain ChE. Inhalation studies with carbaryl and methiocarb are not available at this time. However, dose-response and time-course data via the inhalation route were requested for carbaryl as part of the carbaryl IRED. Route specific studies are preferred since they account for route specific kinetic characteristics which may impact chemical potency. In the absence of inhalation studies, oral data are being used in the revised cumulative risk assessment to estimate inhalation relative potency for carbaryl and methiocarb. This introduces uncertainty regarding the estimation of cumulative risk for the inhalation pathway. However, given that these chemicals do not have a port of entry effect, are expected to be rapidly absorbed, and do not require activation, ChE measured from oral studies are not expected to substantially underestimate potency. (Note: Data from dermal and inhalation studies with oxamyl are not provided here because oxamyl does not have residential uses. See Section II.B.5 for selection of index chemical [oxamyl]).

Table I.B-5. Inhalation BMD_{10}s, $BMDL_{10}$s, and potency estimates from rat brain and RBC ChE inhibition for the *N*-methyl carbamates with residential/non-occupational uses

Chemical	Brain		RBC	
	BMD_{10}	$BMDL_{10}$	BMD_{10}	$BMDL_{10}$
Carbaryl[1]	1.58 mg/kg	1.11 mg/kg	5.59 mg/kg	3.41 mg/kg
Methiocarb[1]	1.31 mg/kg	0.56 mg/kg	3.18 mg/kg	0.81 mg/kg
Propoxur[2]	F= 0.0095 mg/L M= 0.016 mg/L (converted to 4.54 mg/kg for RPF calculation)	F= 0.0076 mg/L M= 0.011 mg/L	NA	NA

[1]No inhalation studies are available for carbaryl and methiocarb; potency estimates are from oral studies

[2]Inhalation BMDs and BMDLs for propoxur were different between sexes, therefore are displayed separately. No apparent dose-response for RBC inhalation for propoxur and therefore no BMD.

c. Results: Half Life Time to Recovery

Half-lives for time to recovery from oral studies in adult rats are provided in Table I.B-6. Since brain ChE is the focus of this revised assessment and the preliminary assessment indicated similar recovery for brain and RBC ChE, Table I.B-6 provides only brain half-life estimates. For most of the NMCs, recovery half-life estimates for brain AChE inhibition range from <1 hour up to 4 hours for adults. Recovery half-lives increased with dose for brain AChE in carbaryl studies. No significant sex differences were noted in brain AChE recovery half lives. At higher doses of carbaryl, recovery half-life for oral exposure was estimated to approximately 12 hours. However, at lower doses more relevant for risk assessment purposes, the half-life for carbaryl cholinesterase inhibition was estimated at 1 to 2 hours.

For those NMCs which have data in male and female adult rats, the Agency analyzed both sexes. When male and female data provided statistically similar BMD_{10}s, the data were combined and analyzed jointly. This joint analysis provides a more robust analysis using all the available data. However, female data are not available for methiocarb and propoxur while *in vivo* recovery time course data were not sufficiently robust to estimate brain cholinesterase half-lives for pirimicarb and thiodicarb. Overall, the half-life to recovery data support the use of acute, single day exposures in the NMC cumulative risk assessment.

Table I.B-6. Half-life for time to recovery for adult rats from oral studies for brain ChE inhibition for the *N*-methyl carbamates[1]

Chemical	Brain	
	Recovery Half-Life Estimate (hrs)	Lower & Upper Confident Intervals (hrs)
Aldicarb	1.52	1.16-1.99
Carbaryl	1.83	1.23-2.72
Carbofuran	NHEERL 1.65 Registrant 0.68	NHEERL 1.04-2.62 Registrant0.54-0.86
Formetanate HCL	4.26	3.32-5.460
Methiocarb[2]	2.77	1.91-4.01
Methomyl	Registrant (F) 0.67 Registrant (M) 1.05 NHEERL (M) 0.70	Registrant (F) 0.55-0.98 Registrant (M) 0.91-1.23 NHEERL (M) 0.50-0.98
Oxamyl	(F) 0.93 (M) 0.70	(F) 0.78-1.11 (M) 0.58-0.856
Pirimicarb	NA[3]	NA
Propoxur[2]	2.69	1.02-7.04
Thiodicarb	NA	NA

[1]Recovery half-life estimates are presented as a single estimate when there are no differences between sexes and between radiometric and modified Ellman methods, unless otherwise noted; [2] Half-life estimates are for males only; [3]NA: insufficient time course data to estimate brain cholinesterase half-life.

4. Selection of Relative Potency Factors: Brain ChE Inhibition

A key component of cumulative hazard assessment is to select an endpoint pertinent to the common mechanism of toxicity that can be used to quantify cumulative risk. EPA is quantifying cumulative risk to the NMCs using RPFs and PoDs from brain ChE data. As mentioned above, in cases where male and female rats provide similar BMD_{10} estimates, EPA has developed potency estimates jointly (methomyl, pirimicarb and thiodicarb). At the present time, only male data are available for methiocarb, and propoxur. For NMCs where the female and male data provided statistically different results (aldicarb, carbaryl), the male BMD_{10} has been used to calculate relative potency factors since it was the more health protective (i.e., lower) value.

As shown in Table I.B-3, BMD_{10} estimates of brain ChE inhibition were generally similar to those for RBC ChE data. For nine of the ten NMCs (including the most potent NMCs), brain ChE is equally sensitive or more sensitive compared to RBC ChE inhibition. Thus, brain ChE inhibition data provides a health protective endpoint for estimating cumulative risk on both the central and peripheral nervous system. Compared to BMD_{10} estimates based on RBC ChE, BMD_{10} estimates based on brain ChE have tighter confidence intervals and therefore will confer less uncertainty on cumulative risk estimates. Moreover, brain ChE inhibition represents a direct measure of the common mechanism of toxicity as opposed to using surrogate measures (e.g., blood measures).

5. Selection of the Index Chemical (Oxamyl)

OPP's cumulative risk assessment guidance document (USEPA, 2002a) states that the index chemical should be selected based on the availability of high quality dose-response data, preferably in each route of interest, for the common mechanism endpoint and that it acts toxicologically similar to other members of the common mechanism group. High quality dose-response data allows the calculation of PoDs for oral, dermal, and inhalation exposures with confidence. Because the PoDs for the index chemical are used to extrapolate risk to the exposure levels anticipated in the human population, any error or uncertainty in an index chemical's PoD value will be carried forward in the cumulative risk estimates.

a. Candidates for the Index Chemical

When selecting the index chemical, EPA evaluated the availability of quality oral, dermal, and inhalation studies for all ten NMCs. Dermal toxicity studies that provided RBC and whole brain data were available for 4/10 NMCs (carbaryl, methiocarb, oxamyl, propoxur). Inhalation studies were available for only propoxur and oxamyl. At present time, the only NMCs with studies in all three routes of interest are oxamyl and propoxur. As shown in Table I.B-2, the oxamyl database of oral studies is more robust than propoxur. Moreover, the oxamyl dermal study in rabbits provides more robust dose-response data compared to the propoxur rabbit dermal study (Tables 1.B-4 and 1.B-7). Consequently, oxamyl has been selected as the index chemical for the revised cumulative risk assessment of the NMCs.

b. Description of the Oxamyl Database

Oxamyl has a robust oral database that includes 6 acute oral studies (4 registration, 1 NHEERL, 1 human). Radiometric ChE data are available from EPA's NHEERL dose-response and time course studies. A comparative cholinesterase study with juvenile (PND 11) and adult rats is also available (46615301). Doses in oral rat studies ranged from 0.005 to 15.3 mg/kg and

thus provide a broad dose-response range. RBC ChE was measured at the time of peak effect in all six studies. Whole (or half) brain ChE data at peak inhibition are available from the five rodent studies. High quality ChE recovery data in adults and PND11 rats are also available. As shown in Table I.B-3, the brain BMD_{10}s for male and female rats are similar. For both sexes, the confidence limits on the BMD_{10}s also are narrow. Thus, the $BMDL_{10}$s provide robust values for extrapolating cumulative risk.

A double-blind, ascending, single oral dose, human study is also available for oxamyl (MRID 44912301). Mutliple RBC ChE sampling events provided the progression of ChE inhibition, maximum inhibition, as well as enzyme recovery for each volunteer. The human study was examined by the HSRB in April 2006 and deemed scientifically robust and ethically sound for use in risk assessment (HSRB Final Report, June 2006).

Two dermal studies were available for oxamyl, both in the rabbit. Oxamyl exhibited a robust dose-response relationship for assessing cholinesterase activity with RBC and brain. The effect of sex on dose was not significant in either study or compartment. RBC and brain (half-brain) ChE activities for both studies were measured once, at the end of the study. The dermal brain and RBC ChE BMD_{10}s are 34.91 and 64.01 mg/kg, respectively.

An acute (single day, 4 hours) inhalation toxicology study (MRID 45155801) is available for oxamyl. Brain and RBC ChE inhibition were measured at the end of the study. The BMD analyses indicate a robust dose-response relationship for assessing ChE activity with RBC and brain. ChE inhibition was similar for both RBC and brain compartments in both sexes. The inhalation brain and RBC ChE BMD_{10}s are 0.005 mg/L and 0.002 mg/L, respectively.

A detailed description of the benchmark dose analysis for dermal and inhalation studies in oxamyl can be found in Appendix II.B.2. Table I.B-7 provides the brain BMD_{10}s and $BMDL_{10}$s for oxamyl. As the index chemical, it is used to calculate RPFs and PoDs:

- Oxamyl brain **BMD_{10}s** for oral, dermal, and inhalation routes have been used to calculate the oral, dermal, and inhalation *RPFs* for the revised cumulative risk assessment.

- Oxamyl brain **$BMDL_{10}$s** for oral, dermal, and inhalation routes have been used as the oral, dermal, and inhalation *PoDs* in the revised cumulative risk assessment.

Table I.B-7. Oral, dermal, and inhalation brain BMD_{10}s and $BMDL_{10}$s for oxamyl, the index chemical

Endpoint	Oral	Dermal	Inhalation
BMD_{10}	0.24 mg/kg	34.91 mg/kg	0.0047 mg/L
$BMDL_{10}$	0.18 mg/kg	17.05 mg/kg	0.0038 mg/L (converted to 0.66 mg/kg)

6. Relative Potency Factors for the Revised Cumulative Risk Assessment of the *N*-Methyl Carbamates

RPFs were calculated from endpoints for brain ChE inhibition provided in Tables 1.B-3, 1.B-4, 1.B-5, and 1.B-7. An RPF is the ratio of the BMD_{10} of oxamyl divided by the BMD_{10} (or appropriate value) for each NMC. RPFs are listed in Table I.B-8.

Table I.B-8. Relative potency factors for oral, dermal, and inhalation routes[1]

Chemical	Oral RPF	Dermal RPF	Inhalation RPF
Aldicarb	4		
Aldicarb sulfone (Aldoxycarb)[1]	3.44		
Aldicarb sulfoxide[1]	3.68		
Carbaryl	0.15	0.71	0.51
Carbofuran	2.4		
3 & 5-hyrdoxycarbofuran[2]	2.4		
Formetanate HCL	2.18		
Methiocarb	0.18	0.09	0.62
Methomyl	0.67		
Oxamyl	1.00	1.00	1.00
Pirimicarb	0.02		
Propoxur	0.11	0.03	0.18
Thiodicarb	0.89		

[1] Aldicarb sulfone and sulfoxide were not modeled based on metabolite-specific data. Instead they were calculated based on molecular weight conversions from aldicarb assuming equipotent to aldicarb. [2] Carbofuran and 3 and 5-hydroxycarbofuran assumed to be equipotent to carbofuran.

7. Intra-species Variability, Inter-species Extrapolation, and FQPA 10X Safety Factors

Typically, EPA applies standard 10X factors to account for inter-species extrapolation and intra-species variability. The FQPA (1996) also mandates that a 10X safety factor be applied to protect for infants and children unless there is sufficient data to support removal of the 10X. For the revised NMC CRA, *the standard 10X intra-species factor is applied to each of the ten N-methyl carbamates*. The inter-species and FQPA 10X factors applied in the NMC CRA are described below.

a. Inter-species Extrapolation Factor in the revised NMC CRA

The rat provides the basis for the RPFs and PoDs in the cumulative risk assessment for the NMCs. As such, a consideration of inter-species extrapolation is necessary (i.e., animal to human). EPA typically applies a 10X factor to account for differences in animals and humans. In the revised NMC CRA, the Agency has retained the 10X inter-species factor for those seven NMCs with no reliable human cholinesterase data. Oral studies with adult human subjects with measurements of peak RBC ChE inhibition and recovery data are available for aldicarb (MRID 42373001), methomyl (MRID 44721401), and oxamyl (MRID 44912301) and provide the basis for refinement of the inter-species factor for these specific NMCs. These three human studies were evaluated by the HSRB in April, 2006 (HSRB Final Report, June 2006). The Board concluded the human intentional dosing studies were ethical and scientifically robust and appropriate for use by the Agency for purposes of risk assessment. It is noted that the carbofuran human oral study was presented to the HSRB in May 2006; however, the Board concluded that it was not scientifically robust and not useful for risk assessment (HSRB Final Report, July 2006). The revised NMC CRA does not include ChE data from the carbofuran human study. For the acceptable human studies, the RBC ChE data were modeled in a consistent fashion with the rat data to calculate human RBC BMD_{10}s and $BMDL_{10}$s. The Agency then used the RBC BMD_{10} ratios for rats and humans for the pesticide-specific inter-species factor. A comparison of RBC ChE BMD_{10}s and half-life estimates suggests humans are approximately 2-5 times more sensitive than rats with half-life estimates similar between rats and humans (1-2 hours). The oral BMD_{10}s and $BMDL_{10}$s generated from the rat and human ChE data for aldicarb, methomyl, and oxamyl along with the corresponding inter-species factors are provided below in Table I.B-9.

Table I.B-9. Inter-species uncertainty factors and corresponding rat and human BMD_{10}s and $BMDL_{10}$s

Chemical	Rat						Human			Inter-species UF
	Brain			RBC			RBC			
	BMD_{10} (mg/kg)	$BMDL_{10}$ (mg/kg)	½ life (hrs)	BMD_{10} (mg/kg)	$BMDL_{10}$ (mg/kg)	½ life (hrs)	BMD_{10} (mg/kg)	$BMDL_{10}$ (mg/kg)	½ life (hrs)	
Aldicarb	F=0.048 M=0.056	F=0.035 M=0.035	1.5	0.031	0.020	1.1	0.016	0.013	1.7	2X
Methomyl	0.486	0.331	1.0	0.204	0.112	0.8	0.040	0.028	1.6	5X
Oxamyl	F=0.145 M=0.185	F=0.111 M=0.143	0.9	0.278	0.158	0.8	0.083	0.068	2.4	3X

BMD estimates are presented as a single estimate when there are no differences between sexes.
Human RBC data obtained from MRID 42373001 (aldicarb), MRID 44721401 (methomyl), MRID 44912301 (oxamyl).
Rat brain and RBC ChE data obtained for aldicarb from MRIDs 43442302, 43442305, 43829601, 43829602, 45068601; for methomyl from MRIDs 44472001, 44487501, 46646401, Padilla et al. 2007; and for oxamyl from MRIDs 44254401, 44472001, Padilla et al. 2007.

b. FQPA Safety Factor

i. Background

The FQPA (1996) instructs EPA, in making its "reasonable certainty of no harm" finding, that in "the case of threshold effects, **an additional tenfold margin of safety** for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account **potential pre- and post-natal toxicity and completeness of data with respect to exposure and toxicity to infants and children**." Section 408 (b)(2)(C) further states that "the Administrator may use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children."

The FQPA requires that the Agency consider issues related to toxicity and exposure. The text contained in this chapter only considers potential sensitivity of infants and children with respect to toxicity. The risk characterization chapter (I.G) contains a more complete discussion of issues related to exposures from food, water, and in/around the home that could contribute to increased exposure to infants and children relative to adults. However, the Agency believes that there are quality data and scientifically supportable methods to account for specific exposure and behavioral patterns of children. Because characteristics of children are directly accounted for in the exposure assessment and the Agency's methods are not expected to underestimate exposure to NMCs, evaluating the potential for increased toxicity of juveniles is the key component in determining the magnitude of the FQPA factors in the revised NMC CRA.

As described in detail in OPP's cumulative risk assessment guidance, determination of relative toxic potency should be calculated using a uniform basis of comparison, by using, to the extent possible, a common response derived from the comparable measurement methodology, species, and sex for all the exposure routes of interest (USEPA 2001a, 2002a). For the NMCs, estimates of relative potency are required for 10 pesticides. Toxicology studies in the adult rat provide the most extensive cholinesterase activity data for all routes, compartments, and both sexes and as a result provide the basis for the RPFs and PoDs in the NMC CRA. Since adult rat data have been used to derive the RPFs and PoDs, EPA has retained the 10X FQPA safety factor unless reliable data are available addressing the sensitivity of the young such that EPA can determine that a different safety factor value is protective of infants and children. Consistent with the mode of action for NMCs (i.e., neurotoxicity mediated through the inhibition of AChE via carbamylation of the active site), the comparative cholinesterase assays in juvenile and adults provide the most relevant data for evaluating potential sensitivity to infants and children to NMCs.

The Agency has compared the sensitivity of NOAELs (No-Observable-Adverse- Effect-Level), LOAELs (Lowest-Observable-Adverse-Effect-Level), and BMDs from developmental neurotoxicity studies (DNTs) and comparative cholinesterase studies for OPs as well as NMCs. The Agency has three developmental neurotoxicity studies for the NMCs (aldicarb, carbaryl and carbofuran). For every OP and NMC evaluated, the comparative cholinesterase assays (CCA) provide a more sensitive (i.e., lower) endpoint than the respective DNT. In the case of NMCs, the CCA studies are 10-100 fold more sensitive than the DNT studies. Thus, use of AChE inhibition as the endpoint for evaluating the FQPA 10X safety factor is expected to be protective of functional and behavioral effects.

The Agency has focused its evaluation of the FQPA 10X safety factor on post-natal exposure to juvenile rats. In a detailed analysis provided in the OP CRA (USEPA 2006), the Agency showed that following *in utero* exposure to OPs, dams exhibit larger amounts of ChE inhibition compared to fetuses. In other words, protecting against inhibition in the pregnant dams is believed to protect against pup AChE inhibition *in utero*. In contrast to this *in utero* exposure, pups have been shown to be more sensitive than adults in post-natal studies. Thus, data from post-natal exposures in juvenile and adult rats provide the most robust toxicity data for determining the magnitude of the FQPA safety factor for the NMC CRA. The CCA studies provide sensitive and reliable results, and have been identified for use in the cumulative risk assessment as the most appropriate studies for developing the chemical-specific factor to address the potential susceptibility of infants and children to the effects of NMC exposure. Comparative ChE data are available and can be used to derive a chemical-specific factor for use in the cumulative risk assessment to reflect the

differential sensitivity of children and infants compared to adults. For those NMCs without such data, the FQPA 10X safety factor is retained.

As described in detail below, the Agency has used a dose response modeling approach for evaluating quantitatively the relative sensitivity between juvenile and adult rats. In this approach, a BMD was calculated for juvenile and adult brain ChE data. The ratio of the juvenile and adult BMDs from the specific CCA study was calculated—this ratio has been used mathematically as the data-derived, chemical-specific FQPA safety factor. This approach is similar to that used in the OP CRA but different from (although not inconsistent with) approaches used in the single chemical aggregate risk assessments. In single chemical, aggregate risk assessments, the mathematical calculations are more simple and straightforward as only one active ingredient is included. As such, in single chemical risk assessments, when available, data from young or juvenile animals can be (and have been) used directly as the PoD. When the data from the young are used directly in deriving a PoD and the PoD is established based on the most sensitive effects, the FQPA safety factor can be reduced or removed so long as there are no residual concerns regarding potential pre- and post-natal toxicity or concerns regarding the completeness of the toxicity or exposure databases. In the revised NMC CRA, the data-derived FQPA safety factor is used to adjust the chemical specific RPF to account for the potential increased sensitivity of the young.

The Agency has relied primarily on CCA studies in juvenile and adult animals to evaluate the potential sensitivity of young animals to cholinesterase inhibition. Brain cholinesterase inhibition is the focus of this analysis as brain cholinesterase inhibition has been selected as the endpoint for derivation for RPFs and PoDs in the NMC CRA. For each individual NMC, the magnitude of the FQPA 10X safety factor was based on the ChE dose-response data comparing relative sensitivity of adult and juvenile animals. The Agency has also evaluated the recovery data in the young to evaluate the extent to which the young recover from NMC inhibition in comparison to adults (e.g., faster, slower, or similar to adults). If the Agency were to evaluate NMC exposure at shorter intervals than 24 hours (Chapter C), then the Agency would need to account for the half-life to recovery in young animals. The Agency has four CCA studies generated by registrants: carbofuran, formetanate, methomyl, and oxamyl. In addition, NHEERL has provided comparative sensitivity data for aldicarb and carbaryl. The brain BMD_{10} estimates for PND 11 pups span an order of magnitude and are generally 2-3 times lower than adult rats. The half-life estimates for brain inhibition in PND11 rats range from approximately 30 minutes to almost 10 hours compared to 1 to 4 hours in adults. Table I.B-10 displays the BMD_{10} values of both juvenile (PND11 or PND17) and adult rats specifically from the available CCA studies. It is noted that the adult BMD_{10} estimates from the CCA study may be different than the more robust BMD_{10} estimate based on the combined adult data. $BMDL_{10}$ and half-life values for pups are provided for information purposes only.

Table I.B-10. Dose-response and recovery half-life estimates in juvenile and adult rats from comparative cholinesterase studies

Chemical	PND11 Brain			Adult Brain
	BMD_{10} (mg/kg)	$BMDL_{10}$ (mg/kg)	Half-Life (hrs.)	Adult BMD (mg/kg)
Aldicarb[1]	0.017	0.016	NA[2]	0.033
Carbaryl	1.459	1.135	5.4[3]	2.627
Carbofuran	0.039	0.030	3.0	0.109
Formetanate	0.188	0.098	9.5	0.382
Methomyl	0.104	0.070	0.4	0.317
Oxamyl	0.051	0.025	1.5	0.177.

[1]The juvenile rat data for aldicarb is based on a published acute oral neurotoxicity study in PND17 rats (MRID45068601)), [2]Time-course data in juvenile rats not available for aldicarb; [3]The recovery half-life estimate for carbaryl is based on NHEERL data from PND17 pups.

The resulting FQPA safety factor for each NMC is the ratio of the BMD_{10} for adult/pup. Those NMCs without comparative cholinesterase data retain the 10X FQPA safety factor. Since the FQPA safety factor is specific to protecting children and developed from juvenile rat data, it may be applied in the NMC CRA to scenarios specific to children's exposure. The FQPA safety factor is therefore not applied to RPFs for adults. The resulting chemical specific FQPA safety factors for these six NMCs are listed in Table I.B-11.

Table I.B-11. FQPA safety factors for the revised NMC CRA[1]

Chemical	FQPA Safety Factor
Aldicarb	2.0
Carbaryl	1.8
Carbofuran	2.75
Formetanate	2.03
Methomyl	3.05
Methiocarb	10
Oxamyl	3.48
Pirimicarb	10
Propoxur	10
Thiodicarb	10

[1]Those NMCs without juvenile pup data retain the 10X FQPA safety factor

8. Incorporation of Uncertainty/Extrapolation Factors and the Target Margin of Exposure

In general, when performing a cumulative risk assessment using a RPF approach, like that done for the NMCs, uncertainty and extrapolation factors can be incorporated into the risk assessment in two different ways: 1) adjustment of the chemical-specific RPF or 2) incorporation into the target Margin of Exposure. Both ways are used in the NMC CRA.

Adjustment of the Chemical Specific RPF: In cases where the uncertainty or extrapolation factor varies among the chemicals, the chemical-specific RPF is adjusted (i.e., multiplied) by the uncertainty or extrapolation factor. In the case of the NMCs, the FQPA and inter-species factors vary among the chemicals. As such, the Agency has multiplied the FQPA safety and inter-species factors by the RPFs to generate adjusted RPFs for each NMC (Table I.B-11).

Incorporation into the Target Margin of Exposure (MOE): There may be assessments where the magnitude of an uncertainty or extrapolation factor is the same for each member of the common mechanism group. In these assessments, the target MOE identified addresses the total magnitude of the uncertainty or extrapolation factor(s). This is the situation for the intra-species factor in the NMC CRA where the standard 10-fold factor has been applied. As discussed above, both the FQPA safety and inter-species extrapolation factors are accounted for in the adjusted RPFs for the NMC CRA. As such, the target MOE for the NMC CRA is 10 accounting for intra-species variability.

Table I.B-12. Adjusted oral relative potency factors for children and adults based on inter-species and FQPA specific factors

Chemical	Oral RPF	Inter-species Factor	FQPA Factor Children Only	Adjusted RPF Children	Adjusted RPF Adult
Aldicarb	4	2	2	16	8
Aldicarb sulfone (Aldoxycarb)	3.44	2	2	13.8	6.9
Aldicarb sulfoxide	3.68	2	2	14.7	7.4
Carbaryl	0.15	10	1.8	2.7	1.5
Carbofuran	2.4	10	2.75	66	24
5-hydroxycarbofuran	2.4	10	2.75	66	24
Formetanate HCL	2.18	10	2.03	44	22
Methiocarb	0.18	10	10	18	1.8
Methomyl	0.67	5	3.05	10	3.3
Oxamyl	1	3	3.48	10	3
Pirimicarb	0.02	10	10	2	0.2
Propoxur	0.11	10	10	11	1.1
Thiodicarb	0.89	10	10	89	8.9

Table I.B-13. Adjusted dermal relative potency factors for children and adults based on inter-species and FQPA specific factors

Chemical	Dermal RPF	Inter-species Factor	FQPA Factor Children Only	Adjusted RPF Children	Adjusted RPF Adults
Carbaryl	0.71	10	1.8	13	7.1
Methiocarb	0.09	10	10	9	0.9
Oxamyl	1.00	3	3.48	10	3
Propoxur	0.03	10	10	3	0.3

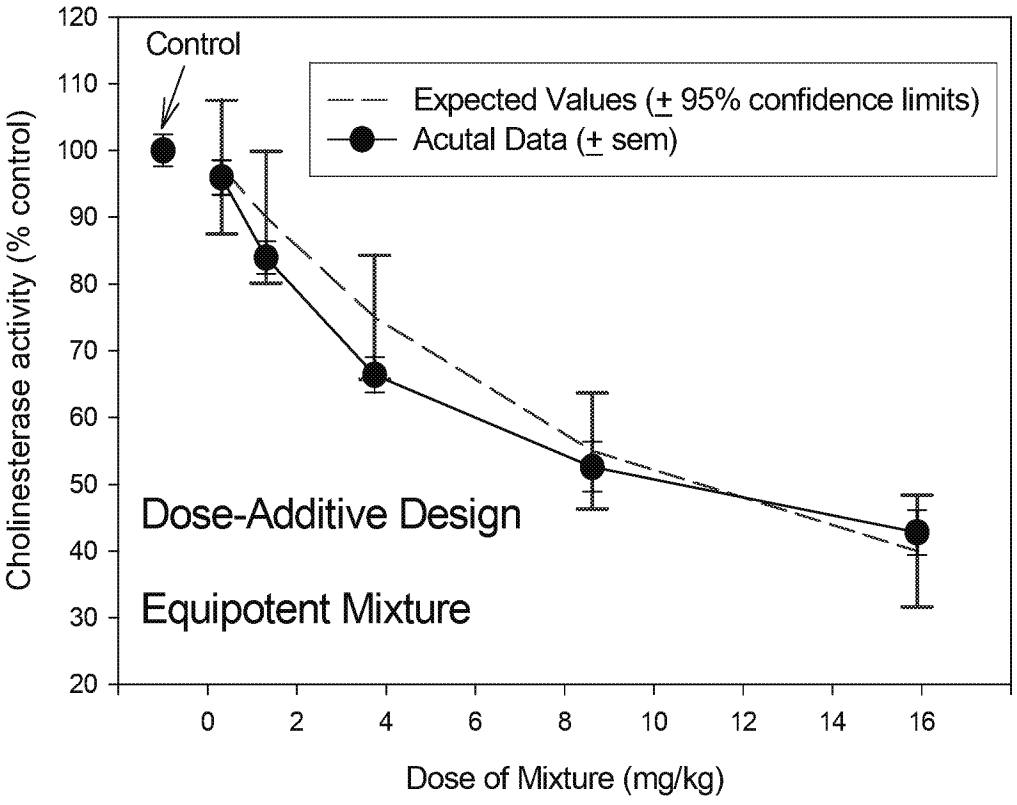
Table I.B-14. Adjusted inhalation relative potency factors for children and adults based on inter-species and FQPA specific factors

Chemical	Inhalation RPF	Inter-species Factor	FQPA Factor Children Only	Adjusted RPF Children	Adjusted RPF Adults
Carbaryl	0.511	10	1.8	9	5.1
Methiocarb	0.619	10	10	62	6.2
Oxamyl	1.00	3	3.48	10	3
Propoxur	0.178	10	10	18	1.8

9. Dose Additivity

A key assumption of the RPF method is dose additivity. While there are a few interaction studies of *N*-methyl carbamate and OP pesticides in the literature (e.g., Gupta and Dettbarn, 1993; Takahashi *et al*., 1987), no studies conducted using mixtures of more than two *N*-methyl carbamates and which use low dose levels (i.e., that do not produce lethality or profound toxicity) have been identified. To fill this data need, NHEERL scientists have conducted a mixture study using seven *N*-methyl carbamates (carbaryl, carbofuran, formetanate HCl, methiocarb, methomyl, oxamyl, and propoxur) (Padilla et al., 2006). In the mixture study, a dose-additive experimental design was used and the proportion of the carbamates in the mixture was based on their potency using the individual-chemical benchmark dose values as the point of comparison. Five different dosage levels of the mixture were given, predicted to produce <5%, 10%, 25%, 45% or 60% brain ChE inhibition. Each NMC was given alone at a previously tested dosage to confirm the original dose-response data (7 single-chemical experimental groups). The effects on motor activity and RBC and brain ChE were measured. As can be seen from **Figure I.B-3** below, increasing dosages of the mixture produced increasing decrements in brain ChE activity. Moreover, the dose-additive model predicted the degree of ChE inhibition within the 95% confidence limits of each predicted value. Additivity was also measured in the RBC ChE and motor activity evaluations (manuscript in preparation).

Figure I.B-3. Plot of brain ChE measured in a seven chemical mixture of *N*-methyl carbamates



10. Summary

This chapter has described the application of the RPF method in the revised cumulative hazard assessment for the NMCs. Whole brain ChE is a sensitive, health protective endpoint representing the target tissue. The brain data provide the most appropriate dataset for extrapolating cumulative risk to this common mechanism group. Potency for the NMCs varies over several orders of magnitude. Analysis of recovery data for brain ChE in adults suggests that half-life time to recovery ranges from less than an hour up to 4 hours is chemical dependant, and for some chemicals, is dose dependant. For some NMCs, recovery of ChE activity in pups may be longer. Overall, the analysis of recovery data supports the Agency's assumption that at the low concentrations found in the environment, the appropriate duration of exposure for the NMC cumulative risk assessment is acute exposure. Oxamyl has been selected as the index chemical based on the availability of high quality dose response data for the oral, dermal, and inhalation routes. $BMDL_{10}$ estimates of brain ChE from oral, dermal, and inhalation studies with oxamyl represent the PoDs for the NMCs cumulative risk assessment. BMD_{10} estimates of brain ChE from oral, dermal, and inhalation studies were used to develop RPFs for the NMCs.

The Agency has, when available, utilized ethically and scientifically valid human studies for refinement of the inter-species factor as well as comparative sensitivity rat data for refinement of the FQPA safety factor. These uncertainty

factors apply to the oral, dermal, and inhalation RPFs, which result in adjusted RPFs for individual NMCs, specifically for adults and children. In instances where there is no human study or comparative sensitivity data for particular NMCs, the inter-species factor and/or FQPA safety factor remain(s) unchanged (i.e., 10x) and is/are used to adjust the RPF accordingly. As a result, the target MOE for the NMC CRA is 10 which accounts for the intra-species 10x factor which is the same for all of the NMCs in the revised NMC CRA.

C. Cumulative Risk from Pesticides in Foods

This chapter discusses the cumulative risk associated with the food exposure pathway. As with previous cumulative assessments released by OPP, the data for this pathway are developed from two primary sources: dietary consumption data collected by USDA's Continuing Survey of Food Intakes by Individuals (CSFII) and pesticide residue monitoring data collected by the USDA Pesticide Data Program (PDP). As described further in Chapter I.B of this document, oxamyl serves as the index chemical and the residue values for the other NMC pesticides were converted to oxamyl equivalents using the RPF approach. The exposure estimates presented in this chapter, therefore, are expressed in terms of the index chemical oxamyl.

The purpose of this chapter is several-fold: (i) to describe and characterize the food consumption, pesticide residue, and other data sources used to develop the cumulative risk assessment for the food pathway; (ii) to describe how and the extent to which the PDP pesticide residue data on approximately 80 food commodities, including those most commonly consumed by children, was extended/translated to other foods in order to produce a more complete data set on pesticide residues that more nearly approximated the total diet; (iii) to describe the methods used to convert pesticide residue data from the PDP data program into index-chemical (i.e., oxamyl) equivalents in order to conduct a cumulative assessment; (iv) to describe how this cumulative residue data set was combined with USDA's food consumption data and food processing data to produce a distribution of estimated cumulative exposures to the NMC group of pesticides; and (v) to provide information with respect to those crop-commodity combinations which contribute to exposure at the upper-ends of the exposure distribution. This chapter does not describe the extensive sensitivity analyses that were performed nor does it provide information on or discuss risk characterization. These are important -- indeed critical -- components of any risk assessment and are presented in Chapter G of this document.

1. Food Consumption Data

Data on food consumption are a necessary component for estimating pesticide exposure through the diet. For the revised NMC CRA, food consumption data were obtained from the USDA CSFII 1994-96/1998 (USDA, 2007). The CSFII 1998 incorporated a supplemental children's survey conducted in 1998 in which the food consumption of an additional 5,559 children (birth through 9 years old) were surveyed. The CSFII 1994-96/1998 is a nationally representative stratified, multi-stage area probability sample with a target population consisting of non-

institutionalized individuals in all 50 states and Washington, DC. CSFII 1994-96/1998 data are derived from information provided by 20,607 individuals who participated in the survey. Individuals who took part in the survey were asked to provide two non-consecutive days of dietary data through the administration of in-person, 24-hour dietary recalls spaced 3–10 days apart. The USDA CSFII consumption survey data are included as an integral component of the DEEM-FCID™ software used to conduct this cumulative risk assessment.[1]

As in previous cumulative risk assessments produced by EPA, separate assessments were conducted on the various sub-populations as represented in the CSFII 1994-96/1998. The current assessment reports on the U.S. general population and the following standard age groups:

- ❑ Infants less than 1 year old
- ❑ Children 1-2 years old
- ❑ Children 3-5 years old
- ❑ Children 6-12 years old
- ❑ Youths 13-19 years old
- ❑ Adults 20-49 years old
- ❑ Adults 50+ years old
- ❑ Females 13-49 years old

[1] It is important to note that the CSFII food diary information is expressed in terms of food *as consumed* (e.g., pizza, apple pie, lasagna, etc.) while OPP's assessments are currently conducted in terms of food *commodities* (e.g., tomatoes, milk, wheat flour, beef, apples, etc.). OPP uses standard recipes to convert foods "as consumed" as reported in CSFII diaries into food commodities for use in OPP dietary risk assessments. The recipe information used to break down the foods was developed jointly by EPA and USDA and is one module in the EPA's Food Commodity Intake (FCID) database which is available upon request. Thus, while this NMC CRA refers to "food" consumption from CSFII, the Agency's calculations are performed in functionally equivalent "food commodity" terms from FCID. While often distinct, "food" and "food commodity" will be used interchangeably in this document.

2. Pesticide Residue Data

There are multiple sources of pesticide residue data (on food) available to EPA. However the sampling design and extent, intent, and representativeness of these various sources of pesticide residue data differ. USDA PDP provides the most comprehensive sampling design, and the most extensive and intensive sampling procedures for pesticide residues of the various data sources available to EPA. Additionally, the intent of PDP's sampling design is to provide statistically representative samples of food commodities eaten by the U.S. population specifically for the purpose of performing dietary risk assessments for pesticides. As such, PDP serves as the only source of pesticide residue data used in quantitative manner in the dietary portion of this revised NMC CRA. The other sources of pesticide residue data are used in a qualitative manner to ensure that EPA is not significantly underestimating pesticide exposure through food. The various sources of pesticide residue data are discussed below.

a. USDA-PDP

As with the preliminary NMC CRA, this revised NMC CRA also relies exclusively on the PDP program for residue data that are used quantitatively. The USDA PDP is a cooperative effort by federal and state agencies to obtain statistically-reliable data on pesticide residues in food (USDA, 2007a). Federal funds support sampling, testing, and data-reporting activities conducted by participating states. The participating states include California, Colorado, Florida, Maryland, Michigan, Minnesota, Montana, New York, Ohio, Texas, Washington, and Wisconsin. In addition, 13 of their neighboring states are in the direct distribution networks of the PDP participating states. Together, these states represent over 50% of the nation's population and all 4 census regions of the U.S. These states also represent the major commercial production areas of fruit and vegetables in the U.S.

The PDP sample collection procedures are specifically designed to produce dietary exposure estimates that closely approximate real world exposures. Samples are collected by USDA at terminal markets and warehouses immediately before these commodities are shipped to supermarkets and other retail establishments. Both domestically produced and imported foods are subject to sampling. Sampling is conducted in accordance with a statistically-based plan designed and put in place by USDA's National Agricultural Statistics Service (NASS) to be representative of the U.S. food supply. Samples are prepared by the analytical laboratory as if for consumption (i.e., they are washed, peeled, and/or cored, as appropriate) and thus are more reflective of actual exposures than data typically available from field trials or FDA monitoring

programs. Thus, measurements simulate as closely as possible dinner-plate exposures to consumers.

The program focuses on high-consumption foods for children and reflects foods typically available throughout the year. A complete description of the PDP program and all data through 2005[2] are available online (USDA, 2007b). The PDP data are available in downloadable electronic format from this site and can be easily transferred, imported, analyzed, and summarized. Appendix II.C.1 lists all of the FCID food commodities for which PDP residue data were used to estimate dietary exposure to NMC pesticides. The PDP residue data on NMC pesticides included in the revised NMC CRA are summarized in Appendix II.C.2.

b. NMC Market Basket Survey

The Carbamate Market Basket Survey Task Force sponsored a market basket survey (MBS) of NMC pesticide residues and their toxicologically relevant metabolites in single-serving samples of fresh fruits and vegetables collected in 1999-2000 (Carringer, 2000). The NMC pesticides analyzed in the MBS were aldicarb, carbaryl, carbofuran, methomyl, oxamyl, and thiodicarb. The food commodities sampled in the MBS were apple, banana, broccoli, grape, head lettuce, orange, peach, and tomato. However, not all NMC pesticides were analyzed in each type of commodity. For instance, aldicarb was analyzed in only one commodity, oranges; and carbaryl was the only NMC analyzed in all eight food commodities. Of the top ten pesticide-commodity combinations contributing to the exposure of young children as determined by this NMC CRA, only two (for children 1-2) and three (for children 3-5) of these significant contributors were sampled in the MBS. Comparing the residue data from the PDP program with the MBS, the top pesticide-commodity contributors common to both MBS and PDP have similar ranges of pesticide concentrations and frequencies of detects. Additionally, PDP has collected more recent data on the same commodities sampled in the MBS. Finally, all of the pesticide-commodity combinations analyzed in the MBS are data for which EPA already has adequate PDP data for the purpose of dietary risk assessment. Consequently, the MBS data have not been used directly in the revised NMC CRA.

c. FDA-CFSAN Pesticide Residue Monitoring Program

[2] Although the 2006 PDP data are not currently available for download from the PDP website, the new data are expected to be published and publicly available in 2007. Due to an active interagency MOU between USDA PDP and USEPA OPP, the 2006 PDP data on NMC pesticides were given priority in PDP's QA/QC process and released early to OPP upon request.

The Food and Drug Administration's (FDA's) Center for Food Safety and Applied Nutrition (CFSAN) Pesticide Residue Monitoring Program is designed primarily for enforcement of EPA pesticide tolerances on imported foods and domestic foods shipped in interstate commerce (USFDA, 2007a). In this monitoring program, domestic samples are generally collected close to the point of production in the distribution system. Import samples are collected at the point of entry into U.S. commerce. The emphasis in sample collection is on the agricultural commodity which is analyzed as the unwashed, whole (unpeeled), raw commodity. Processed foods are also included in the program. Because the emphasis of this program is not on dietary exposure, it is being used in the current assessment mostly as a semi-quantitative check on the potential for residues and as support for data from other sources. The program has extensive data available on eggs and fish, which support the judgment that NMC residues are negligible on these foods as consumed. Thus, the FDA data were used in a qualitative manner in this revised NMC CRA to support the decision to assign residue values of zero to the NMC residues on eggs and fish effectively removing these food commodities from the assessment. Appendix II.C.1 indicates the foods for which such decisions were supported by this program.

d. FDA-CFSAN Total Diet Study

The FDA's CFSAN Total Diet Study (TDS) has provided data on concentrations of contaminants in a wide range of foods for about 46 years (USFDA, 2007b). Foods are purchased at retail (from grocery stores and fast-food restaurants), generally 4 times a year, prepared and cooked for consumption, and analyzed by highly sensitive multi-residue methods. Between 1991 and 2004, there have been 48 market baskets collected. For each market basket, three samples of approximately 280 different foods are collected and composited, and the composite samples are analyzed for – among other things – NMC pesticide residues. A disadvantage of these data is that only one composite sample of each food is analyzed in each market basket. For this reason, these data have been used primarily as semi-quantitative support for judgments on residues in foods.

In previous cumulative risk assessments performed by EPA, conservative estimates of pesticide residue values for some highly consumed foods such as beef were based on the TDS data. However, beef, poultry, and pork are now sampled under the PDP program, being most recently sampled in 2002, 2005, and 2006, respectively. PDP data on these commodities serve as the primary source of residues of pesticides used by EPA in dietary risk assessments, replacing the corresponding FDA TDS data previously used. Both programs have

found very few detects of low concentration NMC residues in these commodities supporting the previous understanding that beef, poultry, and pork are negligible contributors to dietary exposures to the NMC pesticides. The TDS data also includes samples of fish and eggs. The analytical results for these samples confirm those of the FDA surveillance monitoring program, namely, that fish and eggs contain negligible concentrations of NMC pesticides.

3. NMC Pesticides Included in the Food Risk Assessment

The *N*-methyl carbamate Cumulative Assessment Group (CAG) consists of 10 NMC pesticides. These 10 pesticides (along with their ChE—inhibiting metabolites and their associated RPFs) are listed in Table I.C-1.

Table I.C-1. *N*-methyl Carbamates[a] and RPFs

Chemical	RPF (Oral)
Carbaryl[b]	0.15
Aldicarb	4
Aldicarb sulfone (Aldoxycarb)	3.44
Aldicarb sulfoxide	3.68
Oxamyl (Index Chemical)[b]	1
Formetanate hydrochloride	2.18
Methomyl	0.67
Carbofuran	2.4
3-Hydroxycarbofuran	
Propoxur	0.11
Methiocarb	0.18
Thiodicarb	0.89
Pirimicarb	0.02

[a] See "Carbamate Cumualtive Assessment Group: Availability" (USEPA, 2004a).
[b] The carbaryl metabolite, 1-naphthol and the oxamyl metabolite, oxamyl oxime were analyzed by PDP, but not included in the dietary assessment since these compounds are not known to inhibit acetylcholinesterase.

The above listed pesticides and metabolites were used as a "starting point" in determining which pesticides (and associated metabolites) would be considered in the food pathway of the NMC CRA. During the period since the issuance of the preliminary NMC CRA in August 2005, the Agency identified, and in some cases imposed, risk reduction measures on some of the major contributors to carbamate cumulative risk. The risk estimates presented in this revised NMC CRA reflect the risk mitigation measures identified for or taken on individual carbamates since FQPA was signed into law in August 1996. These mitigation measures generally reflect determinations of risk based on the single-chemical risk assessments. For all of the risk mitigation measures that are reflected in this document, EPA has either commenced the processes necessary to implement its selected risk mitigation or intends to commence the appropriate processes in the near future. Having already determined that the identified risk mitigations are warranted for the individual chemicals regardless of the cumulative assessment, EPA has chosen to reflect that mitigation in this assessment. Consequently pesticide-crop combinations that have been (or are being) cancelled or not considered eligible for reregistration[3], do not have food uses, or have had significant and substantial label modifications were excluded from the 1994 to 2006 PDP residue data. As a practical matter, EPA determined that it would serve no purpose to include such uses in the cumulative assessment. Other than by adding a new issue that might delay action, adding these uses would not likely have any impact on the timing or substance of any cancellation decision relating to such uses. And given that the purpose of tolerance reassessment is to determine whether regulatory action should be initiated to modify or revoke tolerances that the Agency finds do not meet the safety standard of section 408, there seems to be little value in including uses in the assessment that will disappear regardless of their impact on cumulative risk, The critical issue for determining whether regulatory action will have to be initiated under section 408 is whether the uses that will remain result in unacceptable dietary risk. EPA recognizes, however, that to the extent that any risk mitigation measures are not subsequently implemented as envisioned in this revised NMC CRA, the cumulative assessment will have to be revised as necessary.

Table in Appendix II.C.2 provides a summary of the PDP samples including the total number of laboratory analyses completed for the NMC pesticides and metabolites on each food commodity in the database.

[3] Although residues resulting from uses that no longer exist were removed from this revised NMC CRA, EPA continues to incorporate violative residues in its cumulative risk assessments to reflect potential exposure to residue not consistent with registered label uses. These violative residues represent pesticide concentrations in PDP samples either above an already existing tolerance level (possibly due to agricultural practices not consistent with label instructions) or in a commodity for which no tolerance has been established.

PDP analytical data for the above pesticides (and their associated metabolites[4], where applicable) are being used in the NMC CRA assessment for the food pathway. Additional details regarding these pesticides and their inclusion in the assessment NMC CRA food pathway assessment are provided below.

Aldicarb: Aldicarb or its sulfoxide and/or sulfone metabolites have been detected in more than 1% of the PDP samples of the following commodities: potato, sweet potato, grapefruit, and orange juice. It has been detected in less than 1% of the samples of the following commodities: green bean, cantaloupe, grape, orange, sweet corn, and poultry liver. PDP reports each of these compounds (all of which are acetylcholinesterase inhibitors) in terms of the parent or specific metabolite *per se*. The metabolites have higher molecular weights than the parent, but the RPF for aldicarb is based on the concentration of the parent chemical. Therefore, the metabolite RPFs were adjusted to account for the higher molecular weight of the metabolites compared to the parent chemical. The conversion of the metabolite concentrations to parent concentrations is important since the majority of detectable aldicarb residues found in PDP commodities are the metabolites.

Carbaryl: Carbaryl has been detected in more than 1% of the PDP samples of the following commodities: apple, apple juice, apple sauce, peach, strawberry, pear, pear juice, grape, grape juice, green bean, orange, nectarine, cantaloupe, carrot, celery, cherry, cranberry, cucumbers, eggplant, grapefruit, orange, orange juice, pineapple, plum, prune, pork fat, pork meat, chicken meat, raisin, rice, spinach, sweet bell pepper, sweet pea, tomato (canned), and asparagus. It has been detected in less than 1% of the samples of the following commodities: banana, broccoli, cauliflower, heavy cream, lettuce, milk, sweet potato, tomato (fresh), watermelon, wheat, and winter squash. Significant label changes, primarily lengthened pre-harvest intervals and reduced application rates, occurred for apple, peach, and strawberry in the late 1990's (Lantz and Young, 2006). These label changes have resulted in lower residue levels for these three crops making only the 2000 and later PDP data relevant. Thus, for the revised NMC CRA, only PDP data for periods during 2000-2006 were used for apple, peach, and strawberry; whereas, the full PDP dataset (1994-2006) was used for all other commodities with carbaryl detects.

Carbofuran: Carbofuran has been detected in more than 1% of the PDP samples of the following commodities: cucumber, kale greens, sweet bell pepper, and wheat. It has been detected in less than 1% of the samples of the following commodities: cantaloupe, grape, grape

[4] The carbaryl metabolite, 1-naphthol and the oxamyl metabolite, oxamyl oxime, were analyzed by PDP, but not included in the dietary assessment since these compounds are not known to inhibit AChE.

juice, green bean, spinach, watermelos, and winter squash. EPA has determined that all domestic carbofuran uses are ineligible for reregistration and this chemical is undergoing cancellation (USEPA, 2006e). Thus, the revised NMC CRA includes only carbofuran uses on the following imported commodities for which tolerances are being retained: bananas, rice, sugarcane, and coffee[5].

Formetanate HCl: Formetanate has been detected in more than 1% of the PDP samples of nectarines and pears. It has been detected in less than 1% of the samples of apples and oranges. Formetanate is analyzed by PDP using a single-residue method and not all PDP commodities have been analyzed using this method. The laboratory performing this analysis ceased participating in the PDP program after 2001. Thus, PDP data are only available for formetanate on orange, pear, nectarine and apple through 2001. Late season uses on oranges, nectarines, and apples were cancelled and field trial data conducted by the registrant using only early-season applications demonstrate that no detectable residues are expected (USEPA, 2006f). Thus, formetanate residues on oranges, nectarines and apples are assumed to be negligible and were not considered in the revised NMC CRA. Only formetanate use on pear has been included in the assessment, and then only using data from 1997 and 1998.

Methiocarb: Methiocarb has been detected in less than 1% of the PDP samples of cauliflower, cherries, cucumbers, and sweet bell peppers. Methiocarb has not been detected on any other PDP commodities.

Methomyl: Methomyl has been detected in more than 1% of the PDP samples of the following commodities: apple, asparagus, broccoli, cantaloupe, cauliflower, celery, cucumbers, eggplant, grape, green bean, kale greens, lettuce, nectarine, peach, spinach, strawberry, summer squash, sweet bell pepper, and watermelon. It has been detected in less than 1% of the samples of the following commodities: carrot, orange, pear, tomato, and winter squash. PDP data for all crops except grape and strawberry were included in the revised NMC CRA. A voluntary cancellation request has been received by the Agency for methomyl use on grapes, and the strawberry use was voluntarily canceled by the registrant early in 2007. Thus methomyl residues on grapes and strawberries were not incorporated into the assessment. In an effort to better reflect NMC residues on foods as eaten, the PDP lettuce samples were divided into leaf and head where information regarding the lettuce variety was available. Separating the lettuce varieties ensured that leaf lettuce residues, which tend to be higher than head lettuce residues,

[5] Sugarcane and coffee are not assumed to contain residues of carbofuran due to the extensive processing, purification, and refinement to which the commodities are subjected.

were not inappropriately assigned to foods that contain head lettuce as an ingredient, as per the FCID recipe files.

Oxamyl: Oxamyl (parent) has been detected in more than 1% of the PDP samples of the following commodities: cantaloupe, celery, cucumber, eggplant, lettuce, pear, potato, summer squash, sweet bell pepper, tomato and watermelon. It has been deteced in less than 1% of the samples of the following commodities: apples, green bean, orange, spinach, and winter squash. An oxamyl metabolite, oxamyl oxime, also detected in the PDP program, was not considered in the assessment since it does not inhibit acetylcholinesterase.

Pirimicarb: Pirimicarb has been detected on less than 1% of the PDP samples of peach and sweet bell pepper. Pirimicarb has not been detected on any other PDP commodities.

Propoxur: Propoxur has not been detected on any PDP commodities.

Thiodicarb: Thiodicarb has been detected on less than 1% of PDP samples of pear. Thiodicarb has not been found on any other PDP commodities.[6]

4. Food Commodities Included in the Food Risk Assessment

The universe of foods included in the cumulative dietary exposure assessment is defined by the USDA CSFII 1994-96/1998. The CSFII food diary information is expressed in terms of food *as consumed* (e.g., pizza, apple pie, lasagna, etc.). These foods as reported in CSFII diaries are converted to food *commodities* (e.g., tomatoes, milk, wheat flour, beef, apples, etc.) using standard recipes. The recipe information used to break down the foods was developed jointly by EPA and USDA and is one module in the EPA's Food Commodity Intake (FCID) database. Table in Appendix II.C.1 lists all of the FCID food commodities (translated from CSFII foods) in decreasing order of their relative per capita consumption by children 1-2 years old and children 3-5 years old while table in Appendix II.C.5 contains a complete listing of the FCID food commodities *and* food forms (e.g. "Cooked; Fresh or N/S; Cook Meth N/S") in the DEEM-FCID™ software that were included in this

[6] Although the PDP analytical methods usually convert thiodicarb residues to methomyl, the majority of methomyl residues detected in PDP commodities are assumed to be the result of methomyl use rather than thiodicarb use. The basis for this assumption is that the number of registered uses for thiodicarb is much less than those for methomyl and pesticide usage information indicates very low thiodicarb use on food crops for which it is registered. Since methomyl residues resulting in the highest exposures are from food crops for which thiodicarb is not registered, the assumption that all PDP methomyl residues are due to methomyl use (rather than thiodicarb use) is not expected to significantly underestimate dietary exposure to thiodicarb.

assessment. This table also includes summary information on the residue distributions that were prepared from the revised NMC CRA food residue database as input for each food form. The actual DEEM-FCID™ input files and associated residue files will be made available on the internet or upon request via CD-ROM for any interested party.

PDP has an extensive monitoring program that focuses on food commodities commonly consumed by children and includes a variety of fruits, vegetables, meat/poultry/pork products, dairy products, and grains. In all, 80 food commodities monitored by PDP are included in the revised NMC CRA. Food processing factors that reflect reduction or concentration of NMC pesticides in processed foods were applied to food commodities or specific pesticide-commodity pairs in the PDP program to extend these data for use on cooked and processed food/food forms in the analysis. Through the 80 foods commodities directly analyzed by PDP, the revised NMC CRA accounts for approximately 93% of the foods consumed by children 1-2 years of age.

As mentioned previously, the PDP residue data were further extended to other commodities identified as reasonable for translation of pesticide residue data per Agency policy. That is, residue data on commodities which were analyzed by PDP were translated to similar food commodities with registered uses which were not analyzed by PDP. In this way, residues on foods accounting for an additional 1% of the per capita consumption of children 1-2 years of age were estimated using these translated PDP data. For example, cantaloupe melon residues are translated to honeydew melon and peach residues are translated to apricot. Translations were made using HED SOP 99.3 (USEPA, 1999b) as summarized in Table I.C-2.

Table I.C-2. Crop Translations for Pesticide Monitoring Data

Commodity Analyzed	Commodity translated to...	Comments
Potato	Subgroup 1-C	
Carrot	Subgroup 1-A or 1-C	
Head Lettuce	Cabbage, Chinese cabbage Napa (tight headed varieties), Brussels sprouts, radicchio	All have a head morphology best represented by lettuce. All are in Subgroup 5-A except radicchio (4-A).
Broccoli	Cauliflower, Chinese broccoli, Chinese cabbage bok choy, Chinese mustard, kohlrabi	Broccoli better represents these heading, thickly stemmed and/or more branching cole crops than spinach does.
Spinach	Subgroup 4-A, Subgroup 5-B and Subgroup 4-B (except celery and fennel unless a strong case can be made)	Celery and fennel typically are excluded since residues may be higher in these crops due to the whorled, overlapping petioles which may retain spray residues.
Green Bean	Subgroups 6-A and 6-B	
Soybean	Subgroup 6-C	
Tomato or bell pepper	Group 8	All are fruiting vegetables.
Cucumber	Subgroup 9-B	All are cucurbit vegetables; residues in melon and pumpkin expected to be lower because of removal of rind
Cantaloupe or Winter squash	Subgroup 9-A and pumpkin	
Orange	Group 10	Fruit will be peeled before analysis by PDP.
Apple or Pear	Group 11	All are pome fruits.
Peach	Group 12, except cherries (sweet and tart)	All are stone fruits.
Grape	Kiwifruit	Based on similar cultural practices.
Wheat	Group 15, except corn, rice, or wild rice	All are small grain crops or closely related thereto,
Milk	Meat	Metabolism study must indicate that residues in meat, fat, and meat-by-products will likely be equal to or lower than residues in milk. If dermal use is allowed on beef cattle, then it must be permitted and used on dairy cattle as well.

PDP has not analyzed eggs or fish, but surveillance monitoring data from FDA include extensive analysis of eggs and fish and indicate that NMC residues would not be expected to occur in significant amounts on these two foods. Consequently, residues in the revised NMC CRA were assumed to be zero. These foods account for about 2% of the per capita consumption of children 1-2 years old.

PDP has analyzed high fructose corn syrup and found no NMC residues but has not analyzed any other sugar or syrup sources. The FDA TDS has analyzed refined sugar and maple sugar and found no NMC residues in 46 market baskets surveys (FDA, 2007b). Knowledge of the highly refined nature of sugars and syrups supported by the limited residue data mentioned above is the basis for assuming that negligible residues of NMC pesticides occur in sugars and syrups. Therefore, residues were assumed to be zero for those foods derived from sugarcane, sugar beet, and maple. These foods, in total, account for about 2% of the per capita consumption by children 1-2 years old.

In summary, food forms, not included in the current assessment, account for only slightly more than 2% of the per capita consumption by children 1-2 years of age and the revised NMC CRA accounts for and incorporates almost 98% of the per capita food consumption by 1-2 year old children. No one single food form excluded from the assessment accounts for a significant portion of the consumption. Most of the foods that are not included in the assessment are considered very minor consumption items and include such commodities as mango, sunflower seed, peppermint, and pomegranate.

5. Method of Estimation of Cumulative Food Risk

The cumulative dietary exposure was estimated using the Dietary Exposure Evaluation Model-Food Commodity Index Database (DEEM-FCID™) software (Exponent, 2007). Estimation of dietary exposure was accomplished by combining distributions of pesticide concentrations on foods from USDA PDP with distributions of food consumption from USDA CSFII. The primary advantage of using distributions of pesticide concentrations and consumption values to assess cumulative exposure is that distributions of exposure values are obtained that represent a distribution of realistic scenarios of exposure that describe both probabilities and magnitudes of multi-chemical cumulative exposure through the food pathway.

a. Overview of Single-Chemical Dietary Risk Assessment Process

The dietary exposure models currently used by the Agency for single-chemical assessments rely upon the food consumption data provided by CSFII consumption survey respondents. For any particular respondent's reported consumption, a Monte-Carlo simulation is performed in which a series of randomly-drawn residue concentrations is selected for each food commodity. The exposure from each food commodity is calculated by multiplying each randomly-selected residue value by the amount consumed, and the total daily exposure is calculated by summing exposures within each individual across all

commodities reported consumed by that individual, as depicted below in Equation (1).

$$\underset{\text{(mg ai/kg bwt)}}{\text{Dietary Exposure}} = \sum_{i=1}^{n} \underset{\text{(gm food/kg bwt)}}{\text{Consumption}_i} \times \underset{\text{(1 kg food/1000 gm food)}}{\text{Unit Conversion}} \times \underset{\text{(mg ai/kg food)}}{\text{Residue}_i} \qquad (1)$$

where n = number of unique foods (or food commodities) consumed

This repeated sampling of pesticide residues is performed 5,000 times for each individual's reported food consumption and produces a distribution of 5,000 potential exposure estimates for each individual respondent. The exposure software keeps track of the total daily exposures for each simulated person-day and applies the corresponding survey weights to project the simulated person-days to a per capita level. It is from this distribution of total daily exposures that the exposure at any given percentile (e.g., 95th, 99th, or 99.9th) can be estimated.

b. NMC Food Residue Database

Equation (1) above is, in principle, fairly basic: it is the task of performing and keeping account of these necessary calculations -- particularly for a multi-chemical, multi-pathway cumulative assessment -- that can be cumbersome, complex, and tedious. The residue data used in this assessment consist of nearly 790,000 records of analytical data and sample information. The processing factors account for several thousand additional records of information. Calculations and algorithms are complicated by the fact that they must be done in such a manner that the risk assessor can "work backward" from the cumulative assessment results to identify contributors -- and their relative contributions -- to the overall cumulative risk, and such contributors must be able to be identified on a crop, pesticide, or crop-pesticide combination basis. Because of these issues, all the data manipulations performed as part of this cumulative assessment were conducted outside of the DEEM-FCID™ exposure software using relational database techniques in MS Access. The database used to conduct these cumulative residue calculations consists of, among other things, four major data tables[7,8] as follows:

[7] By maintaining all of the calculation inputs in separate tables in the database, it is possible to modify inputs or perform sensitivity analyses by simply replacing or adding data to the appropriate table. For example, a specific chemical can be omitted from the entire process by assigning it a value of zero in the RPF table. Specific chemical-commodity combinations can be selectively omitted by entering a zero value for that pair in the processing factor table. Specific food commodities can be eliminated from the assessment by removing the entries from the translation table.

1) Residue Data: contains essentially all of PDP sample and analyses data for NMC pesticides for the years 1994-2006. The table in Appendix II.C.2 contains summary information of PDP residue data on the NMC pesticides.

2) Processing Factors: contains all relevant processing factors for specific food form/chemical combinations. The table in Appendix II.C.3 is extracted from these data.

3) Relative Potency Factors: contains the relative potency factors for all chemicals of interest. This table also contains the chemical-specific FQPA safety factor and inter-species uncertainty factor, which are also used to adjust the relative potencies of the NMC residues.

4) Bridging (Translations): provides bridging links or translations between PDP commodity codes, such as AP (for "APple") and all corresponding DEEM-FCID™ food forms, such as *Apple, fruit with peel; Uncooked; Fresh or N/S; Cook Meth N/S*. This table also translates surrogate PDP commodities for other food forms, e.g., orange residue data are assigned to lemon food forms as described in the table found in Appendix II.C.4.

These four tables are linked through common fields, including pesticide codes and commodity codes. Calculation queries are coded into the MS Access database so that all the pertinent PDP samples records can be extracted, each calculation outlined above can be performed, and the results can be sorted and output in various formats for further analysis. A cumulative residue calculation query performs the cumulative calculations (described in the next section), extracting the various parameters needed from the four tables described above. The calculation is performed on all of the food samples that are of interest and the results are compiled in text files containing the cumulative distributions for each food commodity of interest. Each text file contains a header with sample information (number of values, number of detects, number of zeros, average of residues) and all cumulative residue values for a single food form, sorted in descending order. This permits the complete history of each cumulative residue value in the exposure assessment to be traced back to its origins. In this way, all of the sample collection and analytical information associated with a given PDP sample and all arithmetic adjustments used to produce a cumulative residue estimate can be traced to permit sensitivity analyses or food commodity contribution analyses to be performed.

[8] The NMC food residue database is based on the same design as the one used for the OP CRA (USEPA, 2006a).

c. Manipulation of Residue Data for Exposure Assessment

Equation (1) above describes the fundamental algorithm used to estimate exposure from dietary sources. In the case of a cumulative assessment in which it is important to account for *multiple* pesticides within a food commodity, the formula is modified to account for these multiple chemicals. As seen in Equation (2) below, the residues are expressed in (i.e., converted to) index-chemical equivalents and Equation (1) re-cast as follows:

$$\underset{\text{(mg ai/kg bwt)}}{\text{Dietary Exposure}_{IE}} = \sum_{i=1}^{n} \underset{\text{(gm food/kg bwt)}}{\text{Consumption}_i} \times \underset{\text{(1 kg food/1000 gm food)}}{\text{Unit Conversion}} \times \underset{\text{(mg ai/kg food)}}{\text{Residue}_{IE\,i}} \qquad (2)$$

where n = number of unique foods (or food commodities) consumed

Two changes in terms are evident in this equation which reflects a multi-chemical (cumulative) approach: the term "Residue$_i$" is replaced with "Residue$_{IE,}$" (for index-equivalent residue, or residue expressed in terms of the index chemical oxamyl) and the term "Dietary Exposure" is replaced with the term "Dietary Exposure$_{IE}$" (for index equivalent dietary exposure). More specifically: residues (and the resulting estimated dietary exposures) are represented in this new equation in terms of the **index chemical** (for the NMCs: oxamyl). This re-expression of residues in terms of index chemical equivalents is a fundamental principle of cumulative risk assessment and is used throughout this and all of OPP's cumulative assessments. Such re-expression of residues in terms of the common index chemical is performed through the use of the **Relative Potency Factor** (RPF)[9] described (and derived) in Chapter B of this document. More specifically: the concentration of each pesticide in a given PDP food commodity sample is adjusted by multiplying that concentration by a RPF to obtain the equivalent residue expressed in terms of the index chemical. This new calculated residue is the ***Index Equivalent Residue (Residue$_{IE}$)*** appearing in the above equation and the dietary exposure estimate resulting from combining Residue$_{IE}$ and consumption is the ***Index Equivalent Exposure (Dietary Exposure$_{IE}$)***

The following two-step procedure provides additional detail with respect to how this calculation is performed for an individual PDP sample. This process is repeated for each and every PDP sample included in the food assessment.

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[9] The RPFs are also adjusted to account for the additional sensitivity of children compared to adults and humans compared to rats based on the chemical-specific FQPA and inter-species uncertainty factors, respectively. If additional toxicity data to quantify these safety factors are not available or lacking, a default value of 10 is assigned to each of these safety factors. Refer to Section B for details regarding the calculation of chemical-specific RPFs, FQPA safety factors, and inter-species uncertainty factors

Step 1: For each pesticide in the cumulative assessment group, an Index Equivalent Residue ($Residue_{IE}$) is calculated for every residue in a particular PDP sample by multiplying the residue value by the chemical-specific processing factor (PF_i) for the food form of interest and the chemical-specific Relative Potency Factor (RPF_i):

$$Residue_{IE\,i} = Residue \times PF_i \times RPF_i \qquad (3)$$

where i indicates an individual pesticide in the cumulative assessment group

Step 2: The cumulative $Residue_{IE}$ for an individual PDP sample is then calculated by summing the individual $Residue_{IEi}$ of all the pesticides in the cumulative assessment group found in that sample:

$$Cumulative\ \ Residue_{IE} = \sum_{i=1}^{n} Residue_{IE\,i} \qquad (4)$$

where n = the number pesticides in the cumulative assessment group

The above-described procedure is critical in maintaining sample-by-sample integrity. By summing residues expressed in index-chemical equivalent concentrations on a sample-by-sample basis, capturing the co-occurrence of residues on the same sample is assured, and the ability to appropriately account for certain pesticides to be used (or not be used) on the same commodity is concomitantly enhanced.

These distributions of cumulative residues (expressed in terms of index chemical equivalents) are treated as distributions of representative residues and linked to all appropriate food forms. Finally, as described previously, these cumulative residues -- now expressed in terms of index-chemical equivalents -- are combined with a distribution of daily food consumption values via a probabilistic, Monte Carlo simulation using the DEEM-FCID™ software. The probabilistic combination of food consumption distributions and food residue distributions produces distributions of estimated exposures for OPP's standard age groups (Infants < 1, children 1-2, children 3-5, children 6-12, youths 13-19, adults 20-49, adults 50+ years old, and females 13-49 years old). This process has been described in public documents and proceedings of the FIFRA Scientific Advisory Panel (FIFRA SAP, 2000a).

d. Assumptions

The input residue data were drawn from the PDP data base. The PDP program tests different commodities for various pesticides in 10 states throughout the U.S. The residue data from 1994 to 2006 were

used in this assessment unless otherwise noted. The assumptions in this revised NMC CRA, which are summarized below, are essentially identical to those used in the preliminary NMC CRA.

1) Although PDP has conducted single-unit sampling for limited crops (e.g., individual apple and pear samples) since 1998, only the residue data from composite samples (e.g., 10 pounds of apples or pears) were utilized in this assessment. Since a single composite sample can contain several individual servings of some foods, it is implicitly assumed that all these single servings have residues no more or less than the composite residue (average value). For this revised NMC CRA, it is assumed that residues reported on composite homogenates adequately reflect the residues in any given single serving contained in that homogenate. Therefore, no attempt was made to "decomposite" residue values to simulate residues that might be present in the single servings contained in the PDP composite sample.

2) PDP generally uses multi-residue methods to simultaneously analyze food commodity samples for several pesticides in single sample[10]. However, occasionally, for various reasons, not every sample is analyzed for every single pesticide. In instances where a pesticide is not analyzed in a sample, the pesticide is assumed to have a residue of zero. Although not every single pesticide is analyzed on every sample, PDP attempts to analyze for pesticides that are registered on the food commodity of interest. For each pesticide, generally only a small percentage (less than 10%) of the samples of a single commodity is not analyzed for all residues.

3) All residue analyses are subject to the limitations of the sensitivity of the analytical methods. Many of the samples analyzed are reported as being below the limit of reliable detection of the analytical method. It is usual practice in Agency single chemical assessments to assume that residues in non-detectable samples are present at one-half the limit of detection (LOD) of the analytical method in samples that were potentially harvested from treated fields. Thus, for purposes of estimating residues in samples reported as less than the LOD, a proportion of the samples equal to the estimated percent crop treated is assigned a residue level of one-half LOD and the remaining samples, which are assumed to come from untreated crops, are assigned a residue value of zero. This procedure becomes problematic for a cumulative assessment. It is not enough to simply estimate the percent crop treated for each of the pesticides in the cumulative assessment; it is also important to consider the potential for co-occurrence of residues of multiple residues on the same crop. In the case of the NMC pesticides,

[10] The table in Appendix II.C.7 contains summary information with respect to the co-occurrence of NMC pesticide residues in the PDP commodity samples.

we assessed the impact of incorporating one-half LOD values for non-detects in the cumulative assessment. The food portion of the NMC assessment was conducted using the two extreme default assumptions: all non-detects = 0, and all non-detects = ½LOD for the chemical most frequently detected in each PDP commodity. The most prevalent detected chemical was selected because it is reasonable to assume that chemical would also have the greatest number of residues below the LOD. The result of this comparison confirmed that the assumption of zero values for all non-detects did not significantly impact on the results at the higher end of the cumulative exposure distributions. For additional information regarding this sensitivity analyses, refer to the Risk Characterization chapter.

4) The sample-by-sample method of summing residues relies on the PDP sampling procedures to adequately capture the temporal and geographic variations in agricultural practices and pesticide use. This procedure recognizes that the PDP sampling protocols are designed in such a way as to reflect the foods available to the public for consumption in different regions of the country throughout the year.

5) This assessment uses PDP residue data collected over a 13 year period, (1994-2006) to maximize the number of food commodities in the assessment and to minimize the sensitivity of exposure estimates to year-to-year variations in pesticide usage (e.g., atypical pesticide residues in a commodity due to unusual pest pressures). However, including pesticide residues over an extended period of time introduces an issue related to temporal correspondence of pesticide residues in various food commodities. Since PDP cannot sample every commodity every year, OPP relies upon residues in food samples collected in different years. In some cases, the residues in one food may be only one or two years older than residues in another food. In other cases, the food residues may have been sampled several years apart. Temporal correspondence of pesticide residues may be important to consider since acute dietary assessment consider foods eaten over relatively short time period, such as 24 hours. For example, it is not readily obvious if it is appropriate to model 24-hour dietary exposure based on pineapples grown in 2002 and cranberries grown in 2006.

6) In chemical-specific dietary exposure assessments, OPP routinely translates residue data from one food commodity to related ones if the pesticide use patterns are similar on these commodities. For example, data on cantaloupe are often used as surrogate data for honeydew and other melons. For a cumulative assessment, in which a grower has a choice of several chemicals from the cumulative assessment group, these translations of data become more difficult. In the revised NMC CRA, translations of the residue data were made using

the surrogation scheme in HED SOP 99.3 (USEPA, 1999b) to ensure representation of the maximum number of commodities possible. The cross walk between crops is presented in the table in Appendix II.C.4.

6. Estimation of Acute Exposure Using DEEM-FCID™ Software

Residue distribution files were entered in the DEEM-FCID™ software for a Monte Carlo analysis. The Monte Carlo analysis was conducted by an iterative process of multiplication of residue concentrations on foods, expressed in index chemical equivalents, by one-day consumption of these foods, as reported by all individuals in CSFII. This process used all individuals reporting in the consumption survey for both days of the survey and the exposures were calculated as mg/kg body wt/day.

DEEM-FCID™ uses publicly available USDA/EPA recipes for conversion of foods (e.g., lasagna) reported on an "as eaten" basis in the survey to the recipes' component commodities (e.g., tomatoes, wheat, beef, milk, etc.) for which residue data are available. The use of DEEM-FCID™ for dietary exposure analysis has been described previously in public, technical briefings on pesticide risk assessments for pesticides in the re-registration process as well as to the FIFRA Scientific Advisory Panel (SAP). The detailed functioning of DEEM-FCID™ has also been described in previous SAP presentations (FIFRA SAP, 2000a).

7. Results

Table I.C-3 summarizes the DEEM-FCID™-generated estimated dietary (food only) exposures from the revised NMC CRA.

Table I.C-3. Summary of Probabilistic Analysis of Distribution of the Cumulative Dietary Exposures and Risk from Use of *N*-Methyl Carbamate Chemicals on Food Crops[a]

	95th Percentile		99th Percentile		99.9th Percentile		
Population	**Exposure (mg/kg)**	**MOE**	**Exposure (mg/kg)**	**MOE**	**Exposure (mg/kg)**	**MOE**	**Percentile at which MOE=10**
U.S. Population	0.0004	404	0.0023	79	0.0115	15	>99.9
All infants < 1 yrs	0.0005	342	0.0024	74	0.0106	16	>99.9
Children 1-2 yrs	0.0013	141	0.0051	35	0.0229	7.9	99.848
Children 3-5 yrs	0.0010	185	0.0044	40	0.0209	8.6	99.870
Children 6-12 yrs	0.0006	323	0.0028	63	0.0145	12	>99.9
Youth 13-19 yrs	0.0003	576	0.0017	106	0.0098	18	>99.9
Adults 20-49 yrs	0.0001	1278	0.0008	236	0.0042	42	>99.9
Adults 50+ yrs	0.0002	1035	0.0009	193	0.0044	40	>99.9
Females 13-49 yrs	0.0004	505	0.0019	97	0.0101	17	>99.9

[a]Exposure is in mg/kg/day of oxamyl equivalent residues.

Exposures and MOEs (Margins of Exposures) are presented for the U.S. General population and the following sub-populations: infants < 1 years, children 1-2 years, children 3-5 years, children 6-12 years, youth 13-19 years, adults 20-49 years, adults 50+ years and females 13-49 years. In addition, the percentile at which the MOE equals 10 is provided. The summary results are provided for three percentiles in the estimated distribution of exposures: the 95th percentile, 99th percentile, and 99.9th percentiles of exposure. The exposure values are expressed in terms of index-chemical equivalents. MOEs range from 7.9 (children 1-2 years) to 42 (adults 20-49 years) at the 99.9th percentile of exposure. For children 1-2 years, an MOE of 10 is reached at the 99.848th percentile; for children 3-5 years, this MOE is reached at the 99.870th percentile.

Table I.C-4, Figure I.C-1 (for children 1-2 years old) and Figure 1.C-2 (for children 3-5 years old) provide additional information with respect to the contributors (in terms of crops, pesticides, and crop/pesticide pairs) to exposure. Appendix II.C.6 provides additional detailed information regarding the relative contribution of all crop/pesticide pairs for children 1-2 years old, the highest exposed sub-population.

Table I.C-4. Relative Exposure Contribution from Foods for Children 1 to 2 Years Old (At 99.8th Percentile of Exposure and Above)

Food	Percent
Potato	28.4%
Peach	14.4%
Strawberry	11.1%
Spinach	10.4%
Watermelon	6.7%
Pear	5.3%
Cucumber	3.4%
Cantaloupe	3.2%
Grape	3.0%
Bean, snap	2.4%
Nectarine	2.2%
Orange	1.7%
Apple	1.6%
Lettuce, head	1.3%
Total	94.8%[a]

[a]No single remaining commodity contributes more than 1% to the total exposure.

Figure I.C-1. Relative Contribution of Crop/Chemical Pairs to Top 0.2 Percentile of Cumulative Distribution for Children 1-2

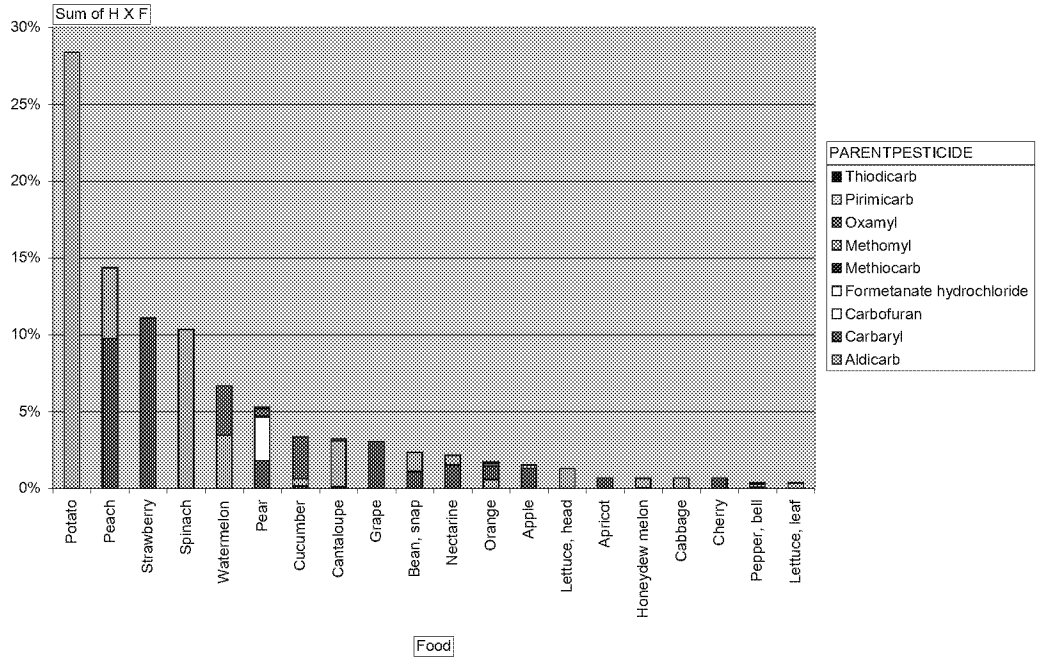
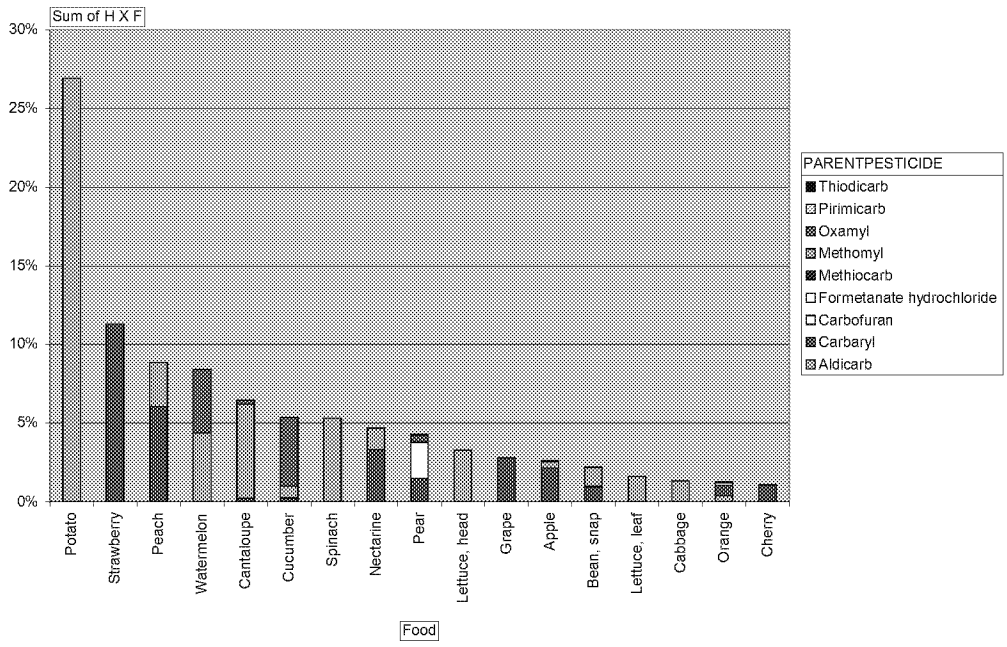


Figure I.C-2. Relative Contribution of Crop/Chemical Pairs to Top 0.2 Percentile of Cumulative Distribution for Children 3-5



In evaluating exposure through food, OPP concludes that a few uses of NMC pesticides on food crops generally play a larger role in the results of the assessment. These include aldicarb on potato; carbaryl on peach and strawberry; and methomyl on cantaloupe, watermelon, peach, spinach, and strawberry. However, evaluation of the total risk from exposure to NMCs in foods indicates that the cumulative MOEs from exposure to NMCs do not raise a concern.

In addition to exposure estimates generated by DEEM-FCID™ software, the Agency has conducted a similar assessment using LifeLine software which is also publicly available. Similar exposure estimates to those generated by DEEM-FCID™ were obtained with this software. It is important to recognize that exposure estimates between DEEM-FCID™ and LifeLine are not expected to be identical since there are important design differences relating to different reference populations, binning methodologies by which each model groups individuals, reference population bodyweights, and model (or sampling) weights. Never-the-less, exposure estimates agree to within several percent. The operation of this software and the exposure estimates produced by LifeLine are described in Appendix II.C.8.

Finally, it is important to note that the exposure estimates and associated MOEs presented in Table I.C-3 represent the Agency's "baseline" assessment described in this on exposure through the food pathway. There are a number of assumptions that are reflected in this baseline assessment that might affect exposure and MOE estimates that are important to consider in evaluating risks associated with this pathway. Specifically:

- The baseline assessment presented here represents virtually all available PDP data (1994-2006)[11] and thus represents an average exposure over this time period. The Agency has performed an equivalent assessment using just the most recent years of PDP (2002-2006), the result of which are discussed in Chapter G. To the extent that more recent PDP pesticide residues more accurately reflect current (and future) conditions, exposure estimates conducted with only this more recent data might be more reflective of the current (and future) risk situation.

- The baseline assessment presented here assumes that PDP samples with non-detectable residues do not contain

[11] Although additional PDP data are available for 1992 and 1993, these data represent the first years of the program which are limited in scope, completeness, and representativeness.

residues (i.e., residues are zero). In reality, residues may be present and – to the extent they are – exposures presented in Table I.C-3 may be underestimates of actual exposure.

- For the baseline assessment, carbofuran was assumed to be present only on commodities with import tolerances (banana, rice, coffee, and sugarcane) since the Agency has determined that all domestic uses are ineligible for reregistration (USEPA, 2006e). Pesticide residue concentrations on uses that are being cancelled were assumed to be zero to represent future carbofuran use.

- The DEEM-FCID™ model does not separate eating events by time and instead sums all eating (and thus exposure) events that occur over a 24-hour time frame. For this Revised NMC CRA, no account is made for the potential reversal of acetylcholinesterase inhibition that would be expected to occur if two or more exposure events are separated in time to such a degree that substantial recovery of AChE inhibition occurs. Such an assumption would be expected to over-estimate risk to the extent that some recovery of AChE activity would occur between exposure occasions.

To account for and evaluate the effect of the above-listed factors on the baseline exposure and risk estimates, the Agency has performed additional analyses which represent "extensions" (sensitivity analyses) to this baseline assessment and permit the Agency to better evaluate how these assumptions and policy choices might affect its exposure and risk estimates. These activities and their results are more fully described in the Risk Characterization chapter of this document.

8. Summary

The cumulative dietary exposure due to the use of NMC pesticides on food crops was assessed using residue monitoring data collected by PDP. Oxamyl was selected as the index chemical and the residue values for the other NMC chemicals were converted to index chemical equivalents using the Relative Potency Factor method. Residue data were collected on approximately 80 food commodities monitored by PDP between the years of 1994 and 2006. Food processing factors were applied to specific chemical-commodity pairs to extend these data for use on more food forms (e.g. boiled, baked, fried, etc.). When appropriate, the PDP residue data were further extended to similar commodities which were not sampled in PDP. Food consumption data

were obtained from the USDA Continuing Survey of Food Intakes by Individuals (CSFII), 1994-96/1998.

The residue data were compiled as distributions of cumulative residues of index chemical equivalents that were, after adjustment for processing, summed on a sample-by-sample basis. These residue distributions were combined with a distribution of daily food consumption values via a probabilistic procedure to produce a distribution of potential exposures for the general U.S. population and various sub-populations. The estimated exposures (expressed in oxamyl-equivalents) are shown in Table I.C-3. An analysis of the relative exposure contribution from foods for children 1 to 2 years at or above the 99.8th percentile of exposure is presented in Table I.C-4.

The results of the baseline assessment indicate that all subpopulations, except children 1-2 and 3-5 years of age, exceed an MOE of 10 at 99.9th percentile of exposure. However, an MOE of 10 was reached for children 1-2 and 3-5 at the 99.848th and 99.870th percentiles of exposure, respectively. EPA concludes that the cumulative MOEs from exposure to NMCs in foods do not raise a concern. (Refer to Chapter G on Risk Characterization for a complete discussion of the rationale for this conclusion.)

D. Residential NMC Cumulative Risk

1. Introduction

The Office of Pesticide Programs (OPP) employed a calendar-based model (Calendex™) to address the temporal aspects of the residential use of pesticides. A calendar-based approach provides the ability to estimate daily exposures from multiple sources over time to an individual and is in keeping with two key tenets of aggregate risk assessment: 1) that exposures -- when aggregated -- be internally consistent and realistic; and 2) that appropriate temporal and geographic linkages or correlations/associations between exposure scenarios be maintained. The Calendex™ software allows OPP to delineate the critical timing aspects of seasonal uses of NMC insecticides that result in exposure to pesticides during the year. Calendex also enables OPP to identify potential risks caused by co-occurrence of exposures from multiple routes and pathways (e.g., near simultaneous same-day exposures through drinking water and residential uses). This includes the exposure from home lawn and garden treatments and pesticides used on golf courses.

In the revised NMC CRA, the temporal aspects of residential pesticide applications were evaluated by relying on information from a variety of sources including registered labels, survey data, and publicly available information provided by State Cooperative Extension Services. These information resources were comprehensively used to identify information such as frequency of applications and the seasonal appearance of target pests. OPP also relied on a national pesticide usage diary survey delineating day of application of registered pesticide products. This longitudinal survey also captures incidence of co-occurrence of residential uses of the same pesticide or similar pesticides on the same day. The survey was conducted by the National Family Organization on behalf of the Residential Exposure Joint Venture (REJV). Additional details regarding all use information used in the revised NMC CRA is presented in Appendix II.D.1.

In addition to the use practice and timing information described above, information regarding residues, exposure and standard exposure factors (such as breathing rates and activity duration) are required. In nearly all cases, the residential exposure scenarios in this assessment were developed using proprietary residue and exposure data. Exposure factors such as breathing rates and durations of time spent outdoors were taken from various sources including Agency's Exposure Factors Handbook (USEPA, 1997a). For the majority of residential uses

considered in this assessment, the full range of exposure values – expressed as uniform, log-normal, empirical, or cumulative distributions – are used, where appropriate, rather than relying on point estimates. While the dietary and drinking water assessments address only the oral exposure route, the residential assessment considers the dermal and inhalation exposure routes as well as the oral route, which is based on the mouthing behavior of young children.

2. Scope of Regional Assessments

Three NMC pesticides in this cumulative assessment have residential uses: carbaryl, methiocarb, and propoxur. More specifically, the residential uses included in this assessment are:

- carbaryl on turfgrass (residential lawns and golf courses);
- carbaryl on fruit trees, vegetable and flower gardens, and ornamental trees and shrubs;
- carbaryl impregnated pet collars;
- propoxur impregnated pet collars;
- methiocarb use in ornamental gardens as a snail and slug bait.

All other *N*-methyl carbamate residential uses are considered minor contributors to exposure and therefore were not included in this assessment.[12] Additionally, the Agency recently received voluntary cancellation of all propoxur indoor spray uses that may result in non-occupational exposure for children (USEPA, 2007c). Therefore, the

[12] For example, propoxur is registered for several residential uses including; outdoor use as a crack and crevice and spot spray, and indoor uses as a containerized bait, paste, shelf paper, or strip. For the outdoor crack and crevice and spot spray uses, applications are typically made along window sills or in pavement cracks; to ant hills and wasp nests. Additionally, the labels for the shelf paper, paste, and strip products restrict use to inaccessible areas. For instance, the paste products are packaged in a pre-filled disposable syringe. Applications are made by pushing the syringe plunger into cracks and crevices in counters, tables, shelving, drawers, under sinks, and around pipes, stoves, and electrical boxes. The propoxur shelf paper products are used in sewers, cabinets, or storage areas around garbage, under sinks, in basements, or other secluded areas where insects congregate. The containerized bait, paste, strip, and shelf paper products, in addition to the outdoor spot uses, are expected to result in very low exposure and therefore are not included in this assessment. Specifically, since the shelf paper, paste and strips are used only to inaccessible areas; children's dermal or hand-to-mouth exposure is not expected. Because the bait is packaged in a child-proof container, use in and around the home also is expected to result in negligible exposure. Additionally, the use of carbaryl for oyster beds in Washington State was assessed in the carbaryl RED. Since the oyster bed use is restricted to one area of the country, and since the assessment of this use indicated low exposure and risk, this use is considered to be a minor contributor to overall risk and therefore is not included in the revised NMC CRA.

propoxur indoor crack and crevice scenario, included in the preliminary NMC CRA, has been removed from this assessment.

In this revised NMC CRA assessment, only the Southeast region of the United States is considered (see Figure I.D-1 below). While insect growth may slow during the winter months in the South, unlike other regions of the country, there is no period of dormancy. Since the growing season is longer in the South and the associated pest pressures are therefore greater, this assessment provides a worst case estimate of exposure.

Figure I.D-1. Pesticide Cumulative Assessment Regions

3. Residential Scenarios

The Residential Scenarios addressed in this document represent critical NMC uses that have the potential for significant exposure when considered in a cumulative assessment. A brief description of each of the use scenarios covered in this assessment is provided below.

a. Lawn Care

Carbaryl (adult applicator and adult and child post-application exposures)

Carbaryl may be applied by homeowners or professional lawn care operators (LCO). Granular, dust, and sprayable applications can be made by consumers using push-type spreaders, ready-to-use (RTU) shaker cans, and hose-end sprayers respectively. OPP has recently amended the use pattern of carbaryl (see Table II.A). The label changes restrict broadcast lawn application to granular formulations. However, spot treatments with the liquid formulations are permitted. Liquid products will be packaged in ready-to-dispense containers that treat areas of no more than 1000 square feet. The current assessment incorporates the recent label changes for the use of carbaryl on residential lawns.

Dermal and inhalation exposure was assessed for homeowners loading, and applying carbaryl to residential lawns. This assessment also considered dermal post-application exposure for adults and children contacting treated lawns. Additionally, oral non-dietary exposure (hand-to-mouth) was considered for toddlers transferring treated-turf residues from their hands to their mouths. Post-application exposure was assessed for the granular broadcast use of carbaryl but not for the liquid spot treatment uses.

b. Vegetable Gardens

Carbaryl (adult applicator and adult and teenagers post-application exposures)

Dust, liquid, and granular formulations of carbaryl may be applied to garden vegetables using RTU shaker cans, handwands, trigger pump sprayers or hose-end sprayers. (Note that recent label changes require all home garden products formulated as either a dust or a granular to be packaged in ready-to-dispense containers (see Table II.A). Dermal and inhalation exposure was assessed for homeowners mixing, loading, and applying carbaryl to vegetable garden plants based on data for the liquid and dust formulations. The use of liquid and dust data for granular applications is conservative and results in higher estimated exposure. Post-application dermal exposure also was considered for adults and teenagers re-entering treated gardens to harvest vegetables or perform maintenance tasks (such as weeding).

c. Ornamentals

Carbaryl (adult applicator and adult and teenager post-application exposures)

Carbaryl may be applied as a dust to ornamental plants using a RTU shaker can. Note that recent label changes require all home garden products formulated as either a dust or a granular to be packaged in ready-to-dispense containers. Carbaryl may also be

sprayed on ornamentals (flowers, trees and shrubs) using a small handwand or hose-end sprayer. The current assessment evaluated exposure for homeowners applying liquid formulations of carbaryl via the handwand sprayer since chemical-specific applicator data suggests that the handwand sprayer resulted in similar yet higher exposure than the hose-end sprayer. The data used to assess this scenario account for homeowners applying sprays below the waist as well as overhead. Dermal and inhalation exposure was assessed for homeowners mixing, loading, and applying carbaryl to ornamental garden plants. Post-application dermal exposure also was considered for adults and teenagers performing ornamental garden maintenance tasks (such as pruning).

Methiocarb (adult applicator exposure)

Methiocarb may be applied to soil areas in and around ornamentals for the control of snails and slugs. This product is formulated as bait applied as a broadcast application over plant foliage or to the soil surrounding ornamental plants. Exposure from this use is expected to be minimal. Therefore, post-application exposure was not evaluated for this scenario.

d. Fruit Trees

Carbaryl (adult applicator and adult and teenager post-application exposures)

Carbaryl may be sprayed on fruit trees using a handwand or hose-end sprayer. The current assessment considers dermal and inhalation exposure for handwand applications only. Chemical specific applicator data for this use indicate greater exposure resulting from handwand applications than from hose-end sprayers, and therefore is considered to be worst case. Post-application dermal exposure was assessed for adults and teenagers harvesting fruit and performing fruit tree maintenance tasks (such as pruning).

e. Pet Collars

Carbaryl (adult and child post-application exposures)
Propoxur (adult and child post-application exposures)

Carbaryl and propoxur are formulated as impregnated pet collars. Post-application dermal exposure was considered for adults and children contacting (hugging, petting) treated pets. Oral non-dietary exposure also was assessed for toddlers contacting treated pets and transferring residues from their hands to their mouths.

f. Golf Course

Carbaryl (adult and teenager post-application exposures)

Carbaryl is also used on golf course turf. Golf course workers may apply liquid or granular formulations of carbaryl as a broadcast application to fairways, greens and tees. Post-application exposure was assessed for adults and teenagers playing rounds of golf on courses treated with the sprayable formulations of carbaryl.

4. Exposure Routes/Scenarios Considered

The routes of exposure considered in this cumulative assessment varied depending on certain application and post-application exposure activities that were determined to be age group-specific. Since cumulative risk assessments do not include occupational risks, applicator exposure is not assessed for the golf course scenario. However, EPA does perform separate occupational risk assessments for such exposure scenarios. The specific exposure routes and pathways/scenarios are summarized and described in additional detail below in Table I.D-1:

Table I.D-1. Specific Exposure Routes and Pathways/Scenarios

Scenario	Population	Applicator			Post Application		
		Oral	Dermal	Inhalation	Oral	Dermal	Inhalation
Lawn/Turf	Adults		X	X		X	
	Children 1-2				X	X	
	Children 3-5				X	X	
Home Garden	Adults		X	X		X	
	Youth 13-17					X	
	Children 1-2						
	Children 3-5						
Indoor (c&c)	Adults		X	X		X	X
	Children 1-2				X	X	X
	Children 3-5				X	X	X
Pet Collars	Adults					X	
	Children 1-2				X	X	
	Children 3-5				X	X	
Ornamental Plants and Trees	Adults		X	X		X	
	Youth 13- 17					X	
	Children 1-2						
	Children 3-5						
Fruit Trees	Adults		X	X		X	
	Youth 13-17					X	
	Children 1-2						
	Children 3-5						
Golf Course	Adults					X	
	Youth 13-17					X	